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Autoimmune Bullous Diseases

Edited by Müzeyyen Gönül and Seray Çakmak

AUTOIMMUNE BULLOUS DISEASES

Edited by **Müzeyyen Gönül**
and **Seray Çakmak**

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Meet the editors

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Contents

Preface

Autoimmune bullous disorders (ABDs) are a heterogeneous group of rare, severe diseases characterized by varying degrees of mucosal and cutaneous blister formations resulting from antibody activities against the different adhesion structures of the epidermis or the dermal-epidermal junction within the skin and/or mucosa. ABDs are classified into four main groups—pemphigus, pemphigoid, acquired epidermolysis bullosa, and dermatitis herpetiformis—according to the location of the bullae in the skin and the antigens targeted by the antibodies. Each of these disorders has its own characteristics and can cause morbidity and even mortality. We aim to present information to our colleagues in different branches of medicine by discussing the etiopathogenetic, clinical and histopathologic features, and management of these disorders in the nine chapters of this book:

- Introduction to Autoimmune Bullous Diseases
- Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment
- Bullous Pemphigoid
- Acquired Epidermolysis Bullosa and Linear Immunoglobulin A Bullous Dermatosis
- Dermatitis Herpetiformis
- Bullous Systemic Lupus Erythematosus and Cicatricial Pemphigoid
- Histomorphologic and Direct Immunofluorescence Findings of Autoimmune Bullous Disease
- Current Therapy in Autoimmune Bullous Disease
- Wound Care in Immunobullous Disease

We believe that this book will be a valuable reference to students, researchers, dermatologists, and other healthcare professionals interested in autoimmune bullous disorders. We are very grateful to all the authors for their strong effort and patience needed to bring out this book. In addition, we thank our husbands and children for supporting us.

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Chapter 1

Introduction to Autoimmune Bullous Diseases

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Additional information is available at the end of the chapter

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Abstract

Autoimmune bullous diseases are heterogeneous group of disorders characterized by intraepidermal and subepidermal bullae formation. Autoantibodies to major players of skin integrity cause devastating symptoms in autoimmune bullous diseases that may result with morbidity and even mortality in the affected patients. These group of diseases can be categorized by the level of splitting in the skin and by structural proteins that are targeted by autoantibodies. Autoimmune bullous diseases can be divided into four basic subgroups: pemphigus, pemphigoid, epidermolysis bullosa acquisita and dermatitis herpetiformis, although their different subtypes have been defined. In this chapter, the structure and tasks of desmosomes and basement membrane zone, which consist of the major antigens of the skin integrity targeted by autoantibodies, are examined, and the relation of target antigens and autoimmune bullous diseases is discussed.

Keywords: autoimmune bullous disease, autoantibodies, desmosomes, acantholysis, basement membrane zone

1. Introduction

Bullae are formed as a result of the damage of skin integrity due to various reasons, including bacterial or viral infections, trauma, genetic disorders and autoantibodies and fluid accumulation in the different layers of the skin; subcorneal, suprabasilar, dermal-epidermal junction and upper dermis [1]. Autoimmune bullous diseases (ABD) are a heterogeneous group of rare but fatal or debilitating skin diseases characterized by varying degrees of mucosal and cutaneous blister formation due to autoantibodies directed against the structural proteins of epidermis or the dermal-epidermal junction [2, 3]. ABD are classified according to the location of the bullae in the skin and the antigens targeted by the antibodies. They are simply

examined in four main groups: pemphigus, pemphigoid, acquired epidermolysis bullosa and dermatitis herpetiformis [1].

It is important to know the structure of the skin and antigens targeted by autoantibodies in order to better understand the ABD. The epidermal stratified squamous epithelium is a complex structure which includes several layers of keratinocytes. Cohesion among these cells is needed to preserve the epidermal architecture and function [4]. Epidermal integrity is provided by three types of junctional structures: (1) anchoring junctions (desmosomes and adherens junctions), major adhesive cell–cell junctions of epithelial cells that function with each other to hold epithelial sheets together. Both are connected with the cytoskeleton and represent sites of mechanical coupling between cells. (2) Tight junctions (zonula occludens) that constitute a diffusion barrier. (3) Gap junctions, where intercellular channels allowing for the direct exchange of small molecules between cells [4, 5]. While suprabasal, differentiating keratinocytes adhere to each other, undifferentiated basal keratinocytes are anchored to the dermis and interact with extracellular matrix. Basal cell surfaces not in contact with basement membrane have desmosomes which attach adjacent keratinocytes [1].

2. Desmosomes

Desmosomes are disc-like strong cell–cell adhesion complexes that act as anchors linking the intermediate filament (IF) cytoskeletons of neighboring cells in tissues that undergo large amounts of mechanical strain such as the heart and skin [6, 7]. In addition to their adhesive role, desmosomes are dynamic structures that regulate normal physiological processes such as proliferation and differentiation during development, tissue morphogenesis and wound healing [3, 6, 8–10].

Desmosomes are described as small dense nodules at the contact points between neighboring cells. “Desmos” means “bond” and “soma” means “body.” Electron microscopic investigations and newly developed procedures have supplied detailed knowledge about their structures and major protein components [3].

Desmosomes are 0.2–0.5 μm in diameter in human epidermis and consist of dense plaques located symmetrically on the plasma membranes of adjoining cells. Extracellular domain, a dense midline separates the membranes [8, 11].

Desmosomes, calcium-dependent junctions, have five major component proteins such as the desmosomal cadherins (DCs) [desmoglein (dsg) and desmocollin (dsc)], the plakin family [desmoplakins, (DP)], and the armadillo proteins [plakoglobin (PK) and plakophilin (PP)] [6, 8].

2.1. Desmosomal cadherins

Dsg and dsc are desmosomal adhesion molecules, and there are four dsg (1–4) and three dsc (1–3) in different tissues in humans. Dsg2 and dsc2 are present in all tissues that contain desmosomes such as simple epithelia, myocardium and are present in low amounts in basal layer

of complex epithelia like epidermis [4, 6]. While dsg4 is present in both stratified epithelia and hair, dsg1/3 and dsc1/3 are found only in stratified epithelia. Dysregulation of desmosomal cadherins causes skin, hair, heart and digestive tract disorders and cancer because of their roles in epithelial morphogenesis and differentiation [6].

Extracellular domains of dsg and dsc are highly homologous to those of classical cadherin, E-cadherin, which have five extracellular cadherin repeats containing Ca2+ binding sites and a cell-adhesion recognition (CAR) site [4, 8]. The cytoplasmic domains of dsg have a membrane proximal region, including an intracellular cadherin-typical region and a dsg-specific region [8].

Dsg 1 expression is higher in suprabasal layers in the skin epithelium. Dsg1 can support keratinocyte differentiation. Extracellular regions of dsg1 do not play a role in this function; they are needed for adhesion. In the recent years, mutations in dsg1 that cause severe skin dermatitis, multiple allergies and metabolic wasting syndrome (SAM) have been identified [6].

In the epidermis, dsg1 and 3 show inverse distribution patterns, dsg3 is present in high levels in the basal layer but dsg1 is found in low levels in this layer. However, the upper layers have high levels of dsg1 and low levels of dsg3. Therefore, pemphigus foliaceus causes bullae only in the most superficial layers of the skin while pemphigus vulgaris leads to blisters in the basal layers of the skin. Because dsg1 and dsg3 are both found in the intermediate layers, blisters do not typically occur in these layers (compensation hypothesis) [6].

2.2. The armadillo repeat and plakin families of desmosomal plaque proteins

The armadillo-repeat family members which are PG and the PP are characterized by their central arm-repeat domains. PG, together with PP, provides the adhesion of DP to keratin intermediate filaments and mediates important signal transduction pathways and regulates the clustering of desmosomal components [12].

İ. Plakoglobin: PG has three structural components as an N-terminal and a C-terminal domain which are separated by the central 12 arm-repeat domain and is homologous to *b*-catenin. Despite this homology, PG and *b*-catenin are differently distributed at cell–cell contacts. *b*-catenin normally is not a component of desmosomes and is only present in adherens junctions unlike PG [5]. PG plays an important role in heart, skin and hair development. Pg−/− mice show severe cardiac defects and Naxos disease that presents with arrhythmogenic right ventricular cardiomyopathy, wooly hair and keratoderma due to the mutation in the gene encoding PG [8].

ii. Plakophilins: PP are members of armadillo-repeat family, and PP1 was originally isolated as an accessory desmosomal plaque protein in stratified and complex epithelia binding to keratin. Later, PP2 and 3 and their subtypes were defined. PP are present both at desmosomes and in the nucleus [5]. While PP1 is mostly expressed in the suprabasal layer, PP2 is located in lower layers of stratified epithelia and heart [12]. All PP have diverse biological and pathological roles [6]. PP1 has an important role in desmosomal plaque formation and stability. *PP1* mutation causes ectodermal dysplasia-skin fragility syndrome in which skin fragility,

inflammation, ectodermal development abnormalities such as scant hair, hypohidrosis and astigmatism are seen [8]. Also, PP1 is elevated in the head and neck cancers and Ewing sarcoma. Therefore, it has been thought that PP1 regulates cell proliferation and growth.

PP2 has a role in the regulation of actin cytoskeletal dynamics, cell migration and tumorigenesis in addition to modulation of intercellular adhesion. PP2 is a new positive regulator for EGFR activation. Knockdown of PP2 causes the attenuation of EGFR-mediated signals and tumor development [6].

Also, the mutations in *PP2* have been identified as a cause of arrhythmogenic right ventricular cardiomyopathy.

PP3 mutations have not yet been identified in humans but *pp3* deficient mice developed cutaneous inflammation and hair abnormalities [8]. This protein mRNA expression has been found to be significantly higher in gastrointestinal cancer patients than controls. Also, its level increased in advanced stages and metastatic cancer. Moreover, it was found that PP3 was increased in breast and pancreatic cancers [6].

2.3. The desmosomal plakin family proteins

Plakins presents with a family of very large cytolinker proteins of 200–700 kDa. They have important role in the cross-linking of actin microfilaments, microtubules and/or intermediate filaments to each other and provide the connection of adhesive junctions with the cytoskeleton. There are seven identified plakin proteins and four of them, desmoplakin (DP), plektin, envoplakin and periplakin are localized in the desmosomes [5].

i. Desmoplakin: DP is an essential desmosomal component in the connection of desmosomal proteins with intermediate filament (IF) cytoskeleton. DP has a critical role in the heart and skin. Global knockout of DP in mouse causes lethality at embryonic days leading to a dramatic decrease in the desmosome numbers [6].

The N-terminal plakin domain peptide (DP-NTP) is essential to target DP to desmosomal plaques and contains binding sites for PPs and PG. The carboxy terminal domain of DP is composed of three plakin repeat domains (PRDs) named A, B and C and is responsible for the attachment of IF [5, 12]. The molecular interactions within the desmosomal plaque protein network are much complicated. It has been shown that the PP1 head domain acts as a lateral linker and allows the recruitment of additional DP molecules to the desmosomal plaque. Moreover, there is evidence that DP might bind directly to desmosomal cadherins in the absence of PG and PPs. But, in cells expressing PP1 and PG, DP preferentially binds to PP1. While dsg1 is the only desmosomal cadherin that interacts with the PP1 head domain PP2 interacts directly with dsg1 and 2, and dsc1a and 2a. In contrast to PP1, PP2 binds to PG. Together with the different tissue distribution of the PPs, the different binding specificities may be involved in the regulation of the size and cadherin composition of desmosomes and the efficiency of IF binding to desmosomes [5].

Two major isoforms of DP were identified: DP1 and DP2. Both are widely expressed in numerous tissues but DP2 is absent/reduced in the heart and simple epithelia [12]. The loss of DP2

causes a more severe adhesion defect due to mechanical stress [6]. DP2 has a more significant role than DP1 in maintaining the adhesion of keratinocytes [12]. Sarcoendoplasmic reticulum Ca+2-ATPase isoform 2 (SERCA2) regulates DP translocation to sites of cell–cell adhesion and SERCA2 is often mutated in Darier's disease. If mutation in DP leads to complete loss of protein or loss of the IF-binding C terminus, it results in lethal acantholytic epidermolysis bullosa with or without apparent associated cardiomyopathy. DP missense mutation can lead to Carvajal/Naxos syndrome that is characterized by keratoderma, wooly hair and cardiomyopathy [6, 8]. Consequently, desmosome mutations can lead to aberrant gap junctions and abnormal heart and epidermal functions, abnormal barrier homeostasis of skin. The loss of DP may also be associated with some cancers and/or their local invasion because of the loss of desmosomal function [6].

ii. Plectin: Plectin, a huge protein, was an originally IF-binding protein and was identified in hemidesmosomal and focal adhesion structures in the basal membrane of keratinocytes in the basal layer of the skin and striated, smooth and cardiac muscles. Later, it was shown that plectin is also expressed in desmosomes. However, it has an auxiliary role and is not a major component of desmosomes. It has major function in the organization of microtubules, actin and IF by coordinated cross-linking and the regulation of their dynamics. Plectin gene mutation does not cause blistering in the epidermis but cause blister formation in the epidermal basal layer by affecting hemidesmosomes. Plectin gene mutation causes autosomal recessive epidermolysis bullosa simplex (EBS) associated with muscular dystrophy [5].

iii. Envoplakin: Envoplakin was originally identified as a plakin protein family member. It was found along IFs and is partially colocalized with DP at desmosomes in terminally differentiating keratinocytes. Similar to plectin, envoplakin is not a major component of desmosomes. Envoplakin knockout mice normally develop but they have only a slight delay in barrier acquisition. No disorders due to the envoplakin mutations have been defined in humans yet [5].

iv. Periplakin: Similar to envoplakin, periplakin is upregulated during terminal differentiation of keratinocytes in cornified envelope. It is distributed more extensively than envoplakin, but there is little knowledge about its role in other tissues. Plectin, envoplakin and periplakin play a role as auxiliary factors in strengthening IF attachment to desmosomes at the desmosomal plaque [5].

2.3.1. The specificity of desmosomal adhesion

Data have shown that adhesive binding between dsc2 and 3 and dsg2 and 3 are both homophilic and isoform specific. Dsg3 can mediate weak homophilic adhesion. Dsc3 shows homophilic binding. While there is a heterophilic interaction between dsc3 and dsg1, there is no interaction between dsc3 and dsg3 [8].

2.3.2. Desmosomal hyperadhesion

Hyperadhesion, a strongly adhesive state is a distinctive property of desmosomes from other intercellular junctions. Adoption of hyperadhesion is a property of dsc. Keratinocytes proliferate

in low Ca2+ medium but do not contact adjacent cells. At the early stage of desmosomal development, desmosomal adhesion is Ca2+ −dependent, and chelating agents may induce the loss of adhesion and splitting of desmosomes. A rise in Ca2+ concentration induces assembly of AJ and desmosomes and in the late stage, epithelial desmosome becomes resistant to low Ca2+, and hyperadhesion is characterized by Ca2+ independence [5]. Hyperadhesion is associated with the ordered arrangement of the dsc. Phosphokinase (PK) C*a* may regulate Ca2+ dependence and inhibit hyperadhesion. Phosphorylation of desmosomal plaque components or different cytoplasmic signals may cause rearrangement in the plaque and transmit a signal to EC domains [8].

2.3.3. Desmosome assembly

The cell–cell contact and specific adhesive interaction are essential components for desmosome assembly. Any disorders of these components caused by low extracellular Ca2+, antibodies and blocking peptide inhibit desmosomal assembly. It was shown that intercellular adhesion starts in AJ and then stabilized by desmosomes. Antibodies to E and P cadherin block AJ and also inhibit desmosome formation [5]. PG plays an essential role in desmosomal assembly by providing interaction between AJ and desmosomes (cross-talk). Other components of desmosomal assembly are PP, dsc, dsg and DP [5, 8]. However, desmosomal assembly can also be induced by protein kinase C signaling in case of lacking of AJ. In the first step, dsg3 is transported to the cell surface, and in the second step, IF attached and half-desmosome-like structures are developed and they intermediate desmosome formation. If half desmosomes are not finally stabilized by interactions with half desmosomes on the adjacent cells they undergo endocytosis and degrade [5].

3. Desmosomes in diseases

The role of desmosomes in maintaining tissue integrity is defined by the large number of diseases in which one or more of its constituents are impaired [4]. The impairment of adhesive functions of desmosomal cadherins results from either development of autoantibodies against desmosomal cadherins or by gene mutations. Pemphigus is a family of blistering skin disorders caused by autoantibodies against desmosomal cadherins [5].

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are two most common forms of pemphigus family and potentially fatal disorders characterized by blister formation in skin and mucous membranes (in PV) due to the acantholysis, loss of keratinocytes cell–cell adhesion. Immunochemical studies showed that in PV, autoantibodies are immunoglobulin (Ig) G type and are directed against dsg3, 130 kD glycoprotein, or both dsg3 and dsg1, 160 kD antigen [5, 13], while in PF, they directed to only dsg1 [1, 12–14]. IgG1 and 4 type autoantibodies are indicators for active disorder while IgG2 is found in remission [1, 3]. Dsg3 and dsg1 show different expression patterns throughout epidermis. Dsg1 is expressed throughout epidermis and oral mucosa but it is more predominant in superficial epidermis than in deep epidermis. In contrast, dsg3 is expressed throughout the oral mucosa but it is only present in basal and

lower epidermal cells. In PF, anti-dsg IgG antibodies cause blistering in the superficial epidermis, but not in the mucosa or deep epidermis because dsg3 expression compensates loss of function due to the anti-dsg1 antibodies. In PV, anti-dsg3 antibodies cause blister development in the deepest layer of mucosa, where dsg1 expression is minimal. Mucocutaneous type PV results from both anti-dsg1 and anti-dsg3 antibodies [14–16]. But, in this type, diffuse intercellular blisters throughout epidermis do not occur. A cause of it may be that cell–cell adhesion might be weaker at the basal and intermediate suprabasal layers, where there are fewer desmosomes. Another reason may be that the lower layer of epidermis might have better access for autoantibodies which penetrate from the dermis. The main postulate of this monopathogenic theory (compensation theory) is that anti-dsg3 and 1 antibodies-dependent disabling of cell–cell adhesion is adequate to cause detachment of keratinocytes and form the blisters [3, 17]. However, data demonstrated that inactivation of dsg3 gene or depletion of dsg3 from keratinocytes could not induce gross blistering in the skin. In striate palmoplantar keratoderma which is due to N-terminal deletion of dsg1 acantholysis or skin blisters are not seen. Thus, compensation theory is still controversial [3, 15, 18]. Multipathogenic theory works to explain blister formation by multiple hit hypothesis. According to this hypothesis, a simultaneous and synchronized inactivation of physiological mechanisms of cell–cell adhesion causes disruption of epidermal detachment. Non-dsg antibodies may be pathogenic because they cause cell shrinkage, loss of adhesion at keratinocytes and/or proapoptotic signaling [17]. Additionally, IgA and IgE classes of Anti-dsg3 antibodies have been found in the sera of PV patients [3].

T-helper cells have critical role in the formation of pemphigus autoantibodies. Activation of autoreactive T cells (losing self-tolerance to dsg) responsive to pemphigus antigens lead to induction of IgG antibodies from B cells [3, 19]. Autoimmunity to certain epitopes of dsg3, dsg-reactive T and B cells may be seen in normal individuals particularly, the relatives of PV patients. There are dsg3 reactive Th1 cells in healthy relatives but there are Th2 cells in PV patients. Th2 reactive cells are detected at similar frequencies in the acute, chronic active and remittent phases of the disease but Th1 cells are increased in chronic active PV. It was demonstrated that Treg cells were decreased in the serum of PV patients [3, 18]. However, there is no decrease in Treg cells in PV skin lesions because Treg cells accumulate in the skin lesions and the draining lymph nodes. It has been thought that pemphigus autoimmunity can be triggered by Toll-like receptors (TLR) because of the activation of PF by TLR7 agonist, imiquimod [3].

4. Mechanism of acantholysis

It was shown that the number and size of desmogleins are reduced in PV and PF [19]. Data demonstrated that pemphigus autoantibodies bind to conformational epitopes formed by the N-terminal 161 amino acids and stabilized by calcium on desmogleins, and that these binding areas are responsible for the pathogenicity but C-terminal extracellular domain is not the pathogenic domain [14]. Previous data showed that PV IgG most likely directly cause the loss of adhesion via the disruption of desmogleins by steric hindrance (cis or trans interaction)

[12, 13, 18]. Interestingly, the detachment of keratinocytes from each other first occurs in the interdesmosomal area, and desmosomal detachment is seen in late acantholysis. Recent studies have demonstrated that the loss of desmosomal function is not only related to the steric hindrance, it may be related with other mechanisms [5, 13]. PV IgG bound to unassembled desmosomal cadherins does not prevent desmosomal generation rather, it causes internalization and degradation of IgG-antigen complex [15].

It has been shown that polyclonal PV IgG causes the retraction of keratin IF and intercellular detachment in vitro in keratinocytes obtained from wild type mice. But PG has critical importance for keratin retraction and detachment of cells [14]. PV IgG binding results in the depletion of dsg3 from keratinocytes and is followed by its internalization and degradation and depriving the not yet assembled desmosome of dsg3 [12, 14]. This suggestion was supported by the demonstration of a reduction in dsg3 levels in cell lysates. In contrast, some studies showed that dsg3 levels increase in cell lysates due to the reduction of anchorage of dsg3 to the cytoskeleton caused PV IgG antibodies [15]. Recent studies in mice have not shown the loss of dsg3 in split desmosomes or keratin retraction in acantholytic areas and that dsg3 is not depleted from desmosome before acantholysis [14].

Early studies showed that non-lysosomal proteases like plasminogen activator released by antibody binding caused the development of blisters but later, investigations in mice did not support this hypothesis and demonstrated that plasmin and plasminogen activators were not necessary for IgG-mediated acantholysis in mice in PV. Recent studies in vivo and in vitro have shown that selective proteases such as MMPs disrupt the adhesion of keratinocytes leading to proteolysis of adhesion molecules. While dsg3 is digested by MMP-9, a member of MMPs family, cell adhesion molecules like dsg1 and E-cadherin are digested by members of ADAM family of MMP during apoptosis [15]. In cultured keratinocytes, it has been shown that PV IgG induces apoptosis resulting in acantholysis. Apoptotic keratinocytes, reduced antiapoptotic factors and increased proapoptotic factors were detected in the epidermis in PF. Thus, induction of apoptosis may be a primary factor responsible for acantholysis and loss of intercellular adhesion. Caspases, apoptosis enzymes that have a role in acantholysis, are the other proteases. It was shown that activated caspase 3 was found in the epidermis before the blister formation, and it could cleave desmosomal proteins such as dsg1, dgs2 and dsg3. Caspases also cause the disruption of plaque proteins such as PP and DP1 and DP2, plektin and periplakin [8, 15]. Moreover, caspase inhibitors may block blister formation [8]. Shortly, these data suggested that caspases have fundamental role in apoptolysis [15]. FasL and CytC activate both extrinsic and intrinsic apoptotic signaling pathways in keratinocytes treated with PV IgGs [17]. Tumor necrosis factor alpha receptor superfamily member 5 and NADAH dehydrogenase-like protein are involved in the extrinsic and intrinsic apoptotic pathways, respectively [3].

Acantholysis is an active and complex process. Interaction of cell and PV IgG causes activation of phosphatidylcholine-specific phospholipase C, an increase in inositol 1,4,5 triphosphate (IP3) and diacylglycerol production and protein kinase C (PKC) activity. It also causes an increase in intracellular calcium concentration [15]. It has been shown that PV IgG causes serine-phosphorylation of dsg3, and the phosphorylation leads to the loss of PG binding. Data

suggested that PG, a cytoplasmic plaque constituent, plays a critical role in keratin retraction because PG binding is essential for targeting dsg3 to desmosomes [8, 14]. Recently, a lot of protein kinase and signaling molecules, including p38 MAPK, PKC, c-myc, Src, Rho A, PERK, FAK, Akt/mTOR, and cdk2 have been demonstrated [11, 15]. For example, it was shown that p38 phosphorylation facilitates the retraction of IF and detachment of the cells [13]. Desmocollin genes encoded N-glycosylated type 1 transmembrane proteins belong to Ca-dependent cell adhesion molecules of cadherin family. Similar to dsg3, dsc3 is expressed in the basal and suprabasal layers of the epidermis. It was demonstrated that anti-dsc3 antibodies might induce the loss of adhesion of epidermal cells and contribute to blister development in pemphigus. In addition to dsg and dsc3 antibodies, reactivity to dsc1, several muscarinic and nicotinic acetylcholine receptor subtypes, HLA molecules, a number of mitochondrial proteins, thyroid peroxidase and hSPCA1 encoded *ATP2C1* gene were shown. Moreover, anti-non-dsg antibodies may show the synergistic effects with anti-dsg antibodies, in other words, they may potentially amplify the activity of anti-dsg antibodies [17].

Anti-mitochondrial antibodies (AMA) target the mitochondrial nicotinic acetylcholine receptors that prevent apoptolysis in keratinocytes. AMA with anti-dsg antibodies can induce acantholysis, AMA/anti-dsg1 induces subcorneal splitting and AMA/anti-dsg3 induces suprabasal acantholysis. Recent studies showed that FcRn receptors exist on the keratinocytes and are a single target for PV IgG. PVIgG/FcRn complexes become internalized and are transmitted to mitochondria. Mitochondria are damaged via AMA and apoptotic signals are triggered for cell shrinkage. This shrinkage resulting in cytoskeleton collapse is an outcome of energy failure due to the damaged mitochondria [17].

According to a recent hypothesis, anti-dsg antibodies are not the reason but the result because reactivity to dsg1/3 develops in both extracellular and intracellular domains, and this gives rise to the thought that dsg molecules are released to intercellular space from damaged keratinocytes and become available to antigen presenting cells [3]. Consequently, pemphigus autoimmunity is directed to multiple organ-specific and non-organ-specific proteins.

Paraneoplastic pemphigus (PNP) is a rare and serious form of pemphigus. It is different from other OBD because it can affect multiple organs as well as skin [11, 20]. It has unusual clinical features, including severe mucosal involvement, bronchiolitis and a wide range of skin rash (pemphigus-like, bullous pemphigoid-like, erythema multiforme-like, graft versus host disease-like and lichen planus-like) [21]. It also shows unusual histopathological and immunological findings. PNP lesions are extremely painful and may be localized on the palm and soles, conjunctiva and simple squamous epithelia. The lesions are resistant to therapy. PNP is usually associated with malignancies such as lymphoma and leukemia. The mortality rate of PNP is high (90%) [11]. It may also be associated with myasthenia gravis and thymomas [22]. Because of cutaneous and noncutaneous pathologies associated with neoplasia it is called as paraneoplastic autoimmune multiorgan syndrome [21].

In PNP, targets of autoantibodies are more than one: dsgs, dscs, DP1 and 2, bullous pemphigoid antigen (BPAg)1, PF, PP, envoplakin, plectin, epiplakin and alpha-2-macroglobulin-like-1 (A2ML-1) that is a broad range protease inhibitor expressed stratified epithelia and other damaged tissues in PNP [11, 20, 22]. Characteristic autoantibodies in PNP target

the plakin family proteins that are molecules localized in the intracellular plaque of desmosomes and hemidesmosomes [20]. Also, anti-acetylcholine receptor autoantibodies and acetylcholinesterase autoantibodies were detected in 35 and 28% of PNP patients, respectively. High levels of these autoantibodies correlated with dyspnea in PNP patients. These antibodies target not only epidermal proteins but also other antigens in neural and bronchial tissues [22].

It is currently unclear why there are multiple autoantibodies in PNP. In patients associated with thymoma, it has been thought that defective thymocyte maturation might lead to the production of autoreactive T cells that can induce B-cell proliferation and autoantibody production. In hematologic malign tumors, aberrant immunological conditions caused by tumors might cause the production of many autoantibodies [22]. Another theory is that autoantibodies against the neoplastic antigens cross-react to epithelial antigens [21]. In PNP, responsible immunity is not solely humoral immunity, also cellular immunity plays a role in the pathogenesis. Therefore, histopathology shows individual keratinocyte necrosis with lymphocyte exocytosis in addition to deposits of autoantibodies in direct immunofluorescence (DIF) examination [20].

Lymphoid tumors may produce antibodies to desmosome and hemidesmosome components. But this solely cannot be explained with the pathogenesis of PNP. It is thought that tumors may express proteins that cross-react with epithelial proteins such as plakins. Another mechanism is dysregulated cytokine production by the tumor cells. The levels of interleukin (IL)-6 which promotes B-cell differentiation and Ig production is increased in PNP. Epitope spreading may explain antibodies against multiple proteins found in PNP [20].

In PNP, accumulation of activated CD8+ T cells and increased interferon gamma and tumor necrosis factor alpha levels were shown in the epidermis locally. Also, natural killer cells were detected in the affected tissues. Consequently, both humoral and cellular immunity play a role in the development of PNP [20].

Another subtype of pemphigus is IgA pemphigus characterized by IgA antibodies to desmosomal and non-desmosomal keratinocyte cell surface constituents. It has two subtypes: subcorneal pustular dermatosis type in which there are antibodies to dsc1 and very rarely to dsc 2 and 3, and intraepidermal neutrophilic type in which target antigen is still unknown but in rare cases, anti-dsg1 and 3 antibodies are the target antigens [11, 21, 23]. The mechanism of the development of skin lesions is not clear. It is thought that IgA antibodies might bind to the Fc receptor CD89 on monocytes and granulocytes resulting neutrophil chemotaxis and subsequent proteolytic cleavage of keratinocyte cell–cell junction [21]. Recently, IgG/IgA pemphigus which is an overlapping variant of classic IgG pemphigus and IgA pemphigus has been defined. Histopathological findings are acantholysis, blister formation localized on subcorneal or entire layer of epidermis and neutrophilic infiltration [11].

Pemphigus herpetiformis (PH) is a pemphigus form clinically resembling dermatitis herpetiformis and histopathologically pemphigus. In PH, autoantibodies against dsg1, dsg3, both dsg1 and dsg3 and more recently, dsc1, dsc3 and an unknown 178-kDa protein were

recognized. PH autoantibodies may recognize functionally less important epitopes of dsg1 or 3; therefore, it does not lead acantholysis directly. It is thought that autoantibodies cause the attraction of the inflammatory cells to tissue inducing by signaling pathway of cytokine production by keratinocytes [21] (**Table 1**).

Pemphigus form	Target antigens
PV	dsg3 or dsg3 and 1, dsc1, muscarinic and, nicotinic
	acetylcholine receptor, several HLA molecules, hSPCA
	mitochondrial proteins, thyroid peroxidase
	subtypes
PF	dsg1
PH	dsg1, dsg3, dsc 1, dsc3, unknown 178-kDa protein
PNP	dsgs, dscs, DP1 and 2, BPAg1, PF, PP, envoplakin,
	plectin, epiplakin and A2ML-1
IgA pemphigus	
SCP	mostly dsc1 rarely dsc2,dsc3
IEN	mostly unknown, some dsg1, dsg3

Table 1. Pemphigus forms and target antigens.

5. Basement membrane zone

Basement membranes are highly specialized forms of extracellular matrix composed of a distinct set of glycoproteins and proteoglycans [24]. They underlie all epithelia and endothelia, enveloping nerves, muscle fibers, distinct cell compartments and whole organs [24]. Basement membranes of various tissues differ ultrastructurally, biochemically and functionally. They act as substrates for attachment of cells, templates for tissue repair, matrices for cell migration, substratum to influence differentiation, morphogenesis and apoptosis of epithelial cell layers and permeability barriers for cells and macromolecules [25]. Basement membranes consist of *lamina densa*, a central electron-dense region, adjacent to a less dense area which is *lamina lucida* or *lamina rara* [24].

Human skin is the body's largest organ, which provides mechanical and immunological barrier against the external environment [26]. The interface between the lower part of the epidermis and the top layer of dermis is the dermoepidermal basement zone (BMZ) which maintains the structure and integrity of the skin by anchoring the overlying epidermis to the dermal matrix below [27]. The importance of the correct assembly of the components of BMZ for skin integrity is apparent from the multiple skin blistering disorders caused by mutations in genes coding for proteins associated with the epidermal BMZ and from autoimmune

disorders where autoantibodies target these molecules. These proteins are also important in tissue homeostasis, repair and regeneration [28].

The epidermal BMZ can be divided into four zones. The first zone contains the cytoskeleton, hemidesmosomes and plasma membranes of basal keratinocytes. The second zone is lamina lucida which contains filaments connecting hemidesmosomes in basal keratinocytes to the lamina densa. The third zone is lamina densa and the fourth zone is sublamina densa region which contains anchoring fibrils, anchoring plaques and fibrillin containing microfibrils [25, 29]. The biochemical components of BMZ are synthesized by basal keratinocytes and dermal fibroblasts [30]. Molecular components of epidermal BMZ are shown in **Table 2**.

The basal keratinocytes are anchored to the basal lamina via the keratin intermediate filaments and hemidesmosomes. The molecules within the basal lamina connect the basal keratinocyte to the basal lamina which anchors the BMZ to the underlying collagenous matrix of the superficial dermis [31]. Hemidesmosomes are small, regularly spaced electron dense structures on the inner surface of the basal pole of the keratinocytes [32]. They extend from the intracellular compartment of basal keratinocytes to the lamina lucida in the upper portion of the dermal epidermal basement membrane. The intracellular domains within the basal keratinocytes attach to the keratin intermediate filament network, and within the lamina lucida, they are contiguous with anchoring filaments [30]. The anchoring filaments transverse the lamina lucida and insert it into the lamina densa. Beneath the lamina densa, the anchoring fibrils extend beneath the basement membrane within the papillary dermis. The hemidesmosomes, anchoring fibrils and anchoring filaments form the hemidesmosome-anchoring filament complex [25, 32]. The hemidesmosome-anchoring filament complex forms a continuous link between the basal keratinocyte intermediate keratin filaments and the underlying BMZ and dermal components [32, 33].

5.1. Molecular components of epidermal basal membrane zone

5.1.1. Cytoskeleton of basal keratinocytes

5.1.1.1. Keratin 5 and 14

There is a structural framework known as the cytoskeleton within each basal keratinocyte which is composed of three main types of filaments: microfilaments, microtubules and intermediate filaments [31]. Basal keratinocytes express intermediate filament keratins 5 and 14 which are the major keratins in the adult epidermis [32]. Intermediate filaments form an intracellular cytoskeletal network throughout the epidermis and help to maintain the cell shape and epithelial structural integrity both through the formation of a cell scaffold and through their connection to desmosomes and hemidesmosomes [27, 32]. Mutations in genes coding *K5* and *K14* interfere with the assembly of the tonofilament cytoskeleton and connection of intermediate filaments to desmosomes and hemidesmosomes [27]. Autosomal dominant mutations in *K5* and *K14* underlie epidermolysis bullosa simplex (EBS) localized to hands and feet [26].

Cytoskeleton of basal keratinocytes
Keratin 5
Keratin 14
Hemidesmosome-anchoring filament complexes
Plectin
230 kDa bullous pemphigoid antigen (BP230/BPAG1)
Type XVII collagen (180 kDa bullous pemphigoid antigen/BP AG2)
$\alpha 6\ ß_4$ integrin
Tetraspan CD151
Laminin 332
Type XIII collagen
Syndecans 1 and 4
$\alpha 3\ ß_1$ integrin
Lamina densa
Laminin 332 (formerly laminin 5)
Laminin 311 (formerly laminin 6)
Laminin 511(formerly laminin 10)
Nidogen
Type 4 collagen
BM-40/SPARC
Perlecan
Sublamina densa region
Type VII collagen
Type IV collagen
Elastin
Fibulins
Fibrillins
Latent TGF-ß-binding proteins
Linkin
Type III collagen
Type I collagen

Table 2. Molecular components of epidermal BMZ.

5.1.2. Hemidesmosome-anchoring filament complexes

5.1.2.1. Plectin

Plectin is an epidermal plakin protein and is a component of hemidesmosome [34]. In the epidermis, the N-terminal of plectin includes binding sites for the cytoplasmic region of integrin ß4, BP180 and actin filaments and the C-terminal connects to keratin filaments [27]. It plays a key role in linking the keratin filament network to hemidesmosomes at the plasma cell membrane [34]. Mutations in plectin gene lead to various forms of EBS, including EBS associated with muscular dystrophy or with pyloric atresia and EBS-Ogna [27].

5.1.2.2. 230 kDa bullous pemphigoid antigen (BP230/BPAG1e)

The first specific target antigen of circulating autoantibodies identified in bullous pemphigoid patients, 230 kDa bullous pemphigoid antigen, which is also called the bullous pemphigoid antigen (BPAG) 1 isoform e (BPAG1e) is an intracellular, hemidesmosomal protein and a member of plakin family [33].

It is the major component of the hemidesmosomal inner dense plaque [29]. BPAG1e interacts with cytoplasmic domain of type XVII collagen, keratin intermediate filaments, erbin and integrin ß4. It links the keratin intermediate cytoskeleton to multiple hemidesmosome components [32]. The N-terminal of BP230 has a role in the integration of BP230 into the desmosomes and has binding sites for BP180 and ß4 integrin, and the C-terminal has binding sites for intermediate keratin filaments [27].

Though BP230 is a major target antigen in BP, the pathogenic relevance of BP230 in BP is not clear due to its intracellular localization [35]. In a study in 1995 in BPAG1e knockout mice, hemidesmosomes were otherwise normal, but they lacked the inner plate and had no cytoskeleton attached. The cell growth or substratum adhesion was also not affected indicating that BPAG1e was not absolutely essential for hemidesmosome or BMZ assembly. The mice also developed severe dystonia and sensory nerve degeneration [36]. In 2014, Feldrihan et al. demonstrated that antibodies against BP230 were nonpathogenic in experimental models of bullous pemphigoid [37].

5.1.2.3. Type XVII collagen (180 kDa bullous pemphigoid antigen/BP AG2)

Type VII collagen, which is also known as 180-kDa bullous pemphigoid antigen, is a transmembrane collagenous protein which is located within the hemidesmosome and lamina lucida [26, 30]. Its intracellular ligands are plectin, BPAG1e and ß4 integrin, and the extracellular ligands are α6 integrin and laminin 332 [29]. Collagen XVII spans almost the entire length of the BMZ and it is a major component of the hemidesmosome [31]. It is thought to play a role in the structure or stability of anchoring filaments, and it has an important function in maintaining the integrity of dermoepidermal junction [32].

Autoantibodies from patients with BP, pemphigoid gestationis (PG) and linear IgA bullous disease (LABD) target the NC16a domain of BPAG2 and from patients with mucous

membrane pemphigoid (MMP) tend to target the distal carboxy terminus of BPAG2, which extends deeper into basement membrane as well as NC16A [25].

The ectodomain of BP180 can be proteolytically shed from the cell surface through cleavage within the NC16A domain generating neoepitopes and the resulting 120 kDa fragment is LAD-1 that can be further processed into a 97 kDa fragment, which is targeted in linear IgA disease and also in BP and pemphigoid gestationis [35].

Mutations in *COL17A1* gene encoding type VII collagen cause non-Herlitz subtypes of junctional EB [27].

5.1.2.4. $\alpha 6\beta_4$ integrin

Integrins are a family of cell adhesion receptors, which have important roles in ligand binding and signaling [11]. The primary integrin in the cutaneous BMZ is $\alpha 6\beta_4$ integrin, which is critical in the adhesion of basal cells to the underlying BMZ [30]. It links the intracellular hemidesmosomal plaque to the extracellular matrix and plays an important role in initiating signaling pathways involved in cell migration, differentiation and survival. The large intracellular domain of β_4 integrin interacts with cytoplasmic domain of BP180 and provides linkage to keratin filaments via plectin. The extracellular domain of $\alpha 6$ and β_4 integrins provides binding sites for various laminin isoforms, including laminin 332 [27]. Mutations in either $\alpha 6$ or β_4 chains result in autosomal recessive junctional EB associated with pyloric atresia [31].

Autoantibodies against $\alpha 6$ and β_4 integrins have been detected in a subgroup of patients with MMP. Autoantibodies recognizing the $\alpha 6$ subunit were found in patients with oral lesions, and autoantibodies recognizing the ß4 subunit were found in patients with ocular involvement [35].

5.1.2.5. Tetraspan CD151

CD151 is a member of the tetraspanin family of cell surface proteins [28]. It is expressed on the basolateral surface of basal keratinocytes concentrated within desmosomes [27, 28]. The possible interaction partners of CD151 are the $\alpha 3\beta 1$ and $\alpha 6\beta 1$ integrins [32]. CD151 is thought to play a role in the organization and stability of hemidesmosomes by facilitating the formation of stable laminin-binding complexes with integrin $\alpha 6\beta 4$ as well as being involved in cellular signaling [27, 28].

5.1.2.6. Laminins

Laminins are a heterogeneous family of noncollagenous glycoproteins within the lamina lucida/lamina densa of all basement membranes. The laminin molecule is formed by three different polypeptide subunits: α, β and γ [38]. Laminins have a cruciform structure containing both globular- and rod-like segments which are implicated in interactions with other extracellular matrix molecules, like the hemidesmosomal components and type VII collagen, as well as in cell attachment [30]. Laminins are the major components of all the basement membranes along with collagen IV and exist in several isoforms which have been shown to self-assemble

into independent networks that are cross-linked by nidogen and perlecan [38]. To date, 16 laminin isoforms have been identified, and some of the laminin isoforms are expressed in the epidermal BMZ [30, 32]. Laminins 5,6 and 10 are the main epidermal BMZ-specific laminins [32]. Laminins promote basement membrane assembly and maintain cell and tissue integrity. Laminins within basement membranes serve as ligands for overlying cell surface receptors, thereby providing signals regarding the epithelial microenvironment [25]. The integrins, a family of cellular receptors, are major receptors that mediate cell adhesion to laminins [38].

Previously known as laminin 5, laminin 332 (epiligrin, kalinin, nicein, GB3 antigen, BM600) is the major laminin within the cutaneous BMZ [25, 30]. It consists of α3, ß3 and γ 2 laminin polypeptide chains [26]. It is found at the upper lamina densa/lamina lucida border at the base of anchoring filaments [32]. It plays an essential role in dermal-epidermal attachment and can be regarded as a bridge between hemidesmosomal proteins (α6ß4 integrin and type XVII collagen) and the anchoring fibrils (Type VII collagen) on the dermal site [27, 35].

The mutations in *LAMA3*, *LAMB3* and *LAMC2* genes encoding laminin 332 cause Herlitz type of junctional EB [35].

Autoantibodies against laminin 332 mainly directed against the α3 chain and can be detected in 20% of patients with MMP. This subgroup is termed anti-laminin 332 MMP, and it is associated with a solid malignancy in 30% of the cases [35].

Laminin γ 1 is a component of various laminin heterotrimers, including laminin 311, 321 and 511. It has been described as a target in anti-laminin γ1 pemphigoid, previously known as anti-p200 pemphigoid [35].

5.1.2.7. $\alpha 3 ß_1$ integrin

The integrin α3 subunit may dimerize with ß1 integrin in the dermoepidermal junction and contribute to epithelial-mesenchymal signaling [27]. Integrin α3 is a transmembrane integrin receptor subunit that mediates signals between the cells and their microenvironment. Mutations in the gene for the integrin α3 subunit causes an autosomal recessive multiorgan disorder characterized with interstitial lung disease, nephrotic syndrome and junctional EB [39].

5.1.2.8. Nidogen

Nidogens (previously known as entactin) are ubiquitous BM glycoproteins [24, 25]. The predominating nidogen is nidogen-1, and nidogen-2 was discovered as second mammalian isoform [24]. They interact with many other BMZ molecules, in particular with laminin and collagen IV, and their primary function appears to be stabilizing interactions between laminins and collagen IV with the lamina densa [35].

Nidogens are not required for epidermal BMZ formation because of the overlapping functions of many of the BMZ components [31].

5.1.2.9. Type IV collagen

Type IV collagen is found only in basement membranes and consists of three α-chain subunits which can be identical or genetically distinct but structurally related [25, 31]. Collagen IV's

primary role in the basement membrane is structural, as its three-dimensional lattice superstructure forms the basal lamina [31]. It is linked to laminins 5/6/10 complex by nidogen [32]. Collagen IV also has been associated with angiogenesis, tissue remodeling and cancer progression. There are many genetic diseases attributed to collagen IV, including Goodpasture syndrome, Alport syndrome, diffuse esophageal leiomyomatosis, benign familial hematuria [25].

5.1.2.10. Heparan sulfate proteoglycans

Heparan sulfate proteoglycans are glycoproteins which are found at the cell surface and in the extracellular matrix, where they interact with a plethora of ligands [40]. Characteristically, three proteoglycans are present in vascular and epithelial basement membranes, including perlecan, agrin and collagen XVIII [29]. They are present within, just above and just below the lamina densa of the epidermal basement membrane [25]. They can interact with various components of lamina densa, including type IV collagen and nidogen, and they are believed to contribute to the overall architecture of the basement membrane as well as tissue-specific functions [25, 29]. Their high sulfate charge contributes to the negative charge of basement membranes and restricts the permeability of these matrices [25].

5.1.2.11. Type VII collagen

Type VII collagen is the major component of anchoring fibrils, and it provides mechanical strength by linking the basal lamina and the underlying connective tissue [35]. Anchoring fibrils lie beneath the basal lamina, and they are fan-like, cross-banded structures extending into the papillary dermis that form semicircular loops [32]. They extend from the lower part of the lamina densa to the upper reticular dermis [25].

Type VII collagen consists of three identical α-chains that self-organize into a triple-helical collagenous structure. Each triple helical domain is flanked by a noncollagenous N-terminal and a C-terminal [27]. It contains a large globular noncollagenous domain termed NC1 in the amino terminal and a smaller domain termed NC2 in the carboxy terminal [25].

A large number of type VII collagen molecules laterally aggregate to form anchoring fibrils in which NC1 domains bind the lamina densa at one end and either loop back into lamina densa or else connect to anchoring plaques in sublamina densa region [25, 30]. The anchoring plaques are electron-dense structures which contain collagen IV and laminin 332 [29]. Specific subdomains within the NC1 domains have affinity for type I fibrillar collagen in the dermis and type IV collagen in the lamina densa and anchoring plaques. It also interacts with laminin 332 [25].

The importance of anchoring fibrils in securing the adhesion of the dermal-epidermal basement membrane to the underlying dermis is seen in mutations in *COL7A1* encoding type VII collagen which underlie both autosomal dominant and autosomal recessive forms of dystrophic EB in which the blister formation occurs in the sublamina densa region [34].

IgG autoantibodies directed against type VII collagen also results in epidermolysis bullosa acquisita which is a severe, acquired autoimmune bullous disease [41].

Type VII collagen has also been described as autoantigen in a small subgroup of patients with MMP, bullous systemic lupus erythematosus and LABD [35] (**Table 3**).

Basement membrane zone molecules	Acquired subepidermal blistering disease
BPAG1e	Bullous pemphigoid
	Mucous membrane (cicatricial) pemphigoid
	Pemphigoid gestationis
	Linear IgA disease
	Lichen planus pemphigoides
Collagen XVII	Bullous pemphigoid
	Pemphigoid gestationis
	Mucous membrane (cicatricial) pemphigoid
	Lichen planus pemphigoides
	Linear IgA disease
Laminin 332	Mucous membrane (cicatricial) pemphigoid associated with malignancy
Laminin 311	Mucous membrane (cicatricial) pemphigoid
Laminin γ1	Anti-laminin γ1 pemphigoid,
	(anti-p200 pemphigoid)
Integrin α6β4	Mucous membrane (cicatricial) pemphigoid
Type VII collagen	Epidermolysis bullosa acquisita
	Bullous lupus erythematosus

Table 3. Targeted molecules and the corresponding acquired subepidermal blistering disease.

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References

[1] Sticherling M, Erfurt-Berge C. Autoimmune blistering diseases of the skin. Autoimmunity Reviews. 2012;**11**:226-230. DOI: 10.1016/j.autrev.2011.05.017

[2] Oh DD, Zhao CY, Murrell DF. A review of case-control studies on the risk factors for the development of autoimmune blistering diseases. Journal of the European Academy of Dermatology and Venereology. 2016;**30**:595-603. DOI: 10.1111/jdv.13386

[3] Grando SA. Pemphigus autoimmunity: Hypotheses and realities. Autoimmunity. 2012; **45**:7-35. DOI: 10.3109/08916934.2011.606444

[4] Cirillo N. 150th Anniversary series: Desmosomes in physiology and disease. Cell Communication & Adhesion. 2014;**21**:85-88. DOI: 10.3109/15419061.2013.863281

[5] Huber O. Structure and function of desmosomal proteins and their role in development and disease. Cellular and Molecular Life Sciences. 2003;**60**:1872-1890. DOI: 10.1007/s00018-003-3050-7

[6] Broussard JA, Getsios S, Green KJ. Desmosome regulation and signaling in disease. Cell and Tissue Research. 2015;**360**:501-512. DOI: 10.1007/s00441-015-2136-5

[7] Amagai M. Adhesion molecules. I: Keratinocyte-keratinocyte interactions; cadherins and pemphigus. The Journal of Investigative Dermatology. 1995;**104**:146-152

[8] Thomason HA, Scothern A, McHarg S, Garrod DR. Desmosomes: Adhesive strength and signalling in health and disease. The Biochemical Journal. 2010;**429**:419-433. DOI: 10.1042/BJ20100567

[9] Al-Amoudi A, Castaño Díez D, Matthew J, Betts MJ, Frangakis AS. The molecular architecture of cadherins in native epidermal desmosomes. Nature. 2007;**450**:832-839. DOI: 10.1038/nature05994

[10] Čabrijan L, Lipozenčić J. Adhesion molecules in keratinocytes. Clinics in Dermatology. 2011;**29**:427-431. DOI: 10.1016/j.clindermatol.2011.01.012

[11] Celentano A, Cirillo N. Desmosomes in disease: A guide for clinicians. Oral Diseases. 2017;**23**:157-167. DOI: 10.1111/odi.12527

[12] Brooke MA, Nitoiu D, Kelsel DP. Cell–cell connectivity: desmosomes and disease. Journal of Pathology. 2012;**226**:158-171. DOI: 10.1002/path.3027

[13] Saito M, Stahley SN, Caughman CY, Mao X, Tucker DK, Payne AS, Amagai M, Kowalczyk AP. Signaling dependent and independent mechanisms in pemphigus vulgaris blister formation. PLoS One. 2012;**7**:e50696. DOI: 10.1371/journal.pone.0050696

[14] Payne AS, Hanakawa Y, Amagai M, Stanley JR. Desmosomes and disease: Pemphigus and bullous impetigo. Current Opinion in Cell Biology. 2004;**16**:536-543. DOI: 10.1016/j.ceb.2004.07.006

[15] Cirillo N, Al-Jandan BA. Desmosomal adhesion and pemphigus vulgaris: The first half of the story. Cell Communication & Adhesion. 2013;**20**:1-10. DOI: 10.3109/15419061.2013.763799

[16] Patel F, Wilken R, Patel FB, Sultani H, Bustos I, Duong C, Zone JJ, Raychaudhuri SP, Maverakis E. Pathophysiology of autoimmune bullous diseases: Nature versus nurture. Indian Journal of Dermatology. 2017;**62**:262-267. DOI: 10.4103/0019-5154.159620

[17] Ahmed AR, Carrozzo M, Caux F, Cirillo N, Dmochowski M, Alonso AE, Gniadecki R, Hertl M, López-Zabalza MJ, Lotti R, Pincelli C, Pittelkow M, Schmidt E, Sinha AA, Sprecher E, Grando SA. Monopathogenic vs multipathogenic explanations of pemphigus pathophysiology. Experimental Dermatology. 2016;**25**:839-846. DOI. 10.1111/exd.13106

[18] Hammers CM, Stanley JR. Mechanisms of disease: Pemphigus and bullous pemphigoid. Annual Review of Pathology. 2016;**11**:175-197. DOI: 10.1146/annurev-pathol-012615-044313

[19] Schmidt E, Spindler V, Eming R, Amagai M, Antonicelli F, Baines JF, Belheouane M, Bernard P, Borradori L, Caproni M, Di Zenzo G, Grando S, Harman K, Jonkman MF, Koga H, Ludwig RJ, Kowalczyk AP, Müller EJ, Nishie W, Pas H, Payne AS, Sadik CD, Seppänen A, Setterfield J, Shimizu H, Sinha AA, Sprecher E, Sticherling M, Ujiie H, Zillikens D, Hertl M, Waschke J. Meeting report of the pathogenesis of pemphigus and Pemphigoid meeting in Munich, September 2016. The Journal of Investigative Dermatology. 2017;**137**:1199-1203. DOI: 10.1016/j.jid.2017.01.028

[20] Yong AA, Tey HL. Paraneoplastic pemphigus. The Australasian Journal of Dermatology. 2013;**54**:241-250. DOI: 10.1111/j.1440-0960.2012.00921.x

[21] Porro AM, Caetano Lde V, Maehara Lde S, Enokihara MM. Non-classical forms of pemphigus: Pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. Anais Brasileiros de Dermatologia. 2014;**89**:96-106. DOI: 10.1590/abd1806-4841.20142459

[22] Hashimoto T. Production of numerous autoantibodies in paraneoplastic pemphigus. The British Journal of Dermatology. 2015;**172**:849-850. DOI: 10.1111/bjd.13648

[23] Düker I, Schaller J, Rose C, Zillikens D, Hashimoto T, Kunze J. Subcorneal pustular dermatosis-type IgA pemphigus with autoantibodies to desmocollins 1, 2, and 3. Archives of Dermatology. 2009;**145**:1159-1162. DOI: 10.1001/archdermatol.2009.224

[24] Breitkreutz D, Mirancea N, Nischt R. Basement membranes in skin: unique matrix structures with diverse functions? Histochemistry and Cell Biology. 2009;**132**:1-10. DOI: 10.1007/s00418-009-0586-0

[25] Yancey KB. The biology of basement membrane zone. In: Bolognia JL, Jorizzo JL, Schaffer JV. Dermatology. 3rd ed. China: Elsevier; 2012. p.449-459

[26] Salam A, Proudfoot LE, McGrath JA. Inherited blistering skin diseases: Underlying molecular mechanisms and emerging therapies. Annals of Medicine. 2014;**46**:49-61. DOI: 10.3109/07853890.2013.866441

[27] Turcan I, Jonkman MF. Blistering disease: Insight from the hemidesmosome and other components of the dermal-epidermal junction. Cell and Tissue Research. 2015;**360**:545-569. DOI: 10.1007/s00441-014-2021-7

[28] Has C, Nyström A. Epidermal basement membrane in health and disease. Current Topics in Membranes. 2015;**76**:117-170. DOI: 10.1016/bs.ctm.2015.05.003

[29] Bruckner-Tuderman L, Payne AS. Epidermal and dermal adhesion In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolf K. Fitzpatrick's Dematology in Genearl Medicine. 8th ed. United States of America: McGraw-Hill; 2012. p:574-585

[30] McGrath JA, Uitto J. Structure and function of skin. In: Griffiths CEM, Barker J, Bleiker T, Chalmer R, Creamer D, editors. Rooks Textbook of Dermatology. 9th ed. United Kingdom: John Wiley&Sons; 2016:37-84

[31] Vidal EM, editor. The basement memebrane zone: making the connection. 1st ed. Handbook of Photovoltaic Science and Engineering. 2nd ed. Chichester: Wiley; 2011. 1132 p. Available from: http://www.aad.org/education/the-basement-membrane-zone-video-lecture First accessed: 10.09.2017

[32] McMillan JR, Akiyama M, Shimizu H. Epidermal basement membrane zone components: Ultrastructural distribution and molecular interactions. Journal of Dermatological Science. 2003;**31**:169-177

[33] Künzli K, Favre B, Chofflon M, Borradori L. One gene but different proteins and diseases: The complexity of dystonin and bullous pemphigoid antigen 1. Experimental Dermatology. 2016;**25**:10-16. DOI: 10.1111/exd.12877

[34] Bouameur JE, Favre B, Borradori L. Plakins, a versatile family of cytolinkers: Roles in skin integrity and in human diseases. The Journal of Investigative Dermatology. 2014 Apr;**134**(4):885-894. DOI: 10.1038/jid.2013.498

[35] Goletz S, Zillikens D, Schmidt E. Structural proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases. Experimental Dermatology. 2017 Sep 8. DOI: 10.1111/exd.13446

[36] Guo L, Degenstein L, Dowling J, Yu QC, Wollmann R, Perman B, Fuchs E. Gene targeting of BPAG1: Abnormalities in mechanical strength and cell migration in stratified epithelia and neurologic degeneration. Cell. 1995;**81**:233-243

[37] Feldrihan V, Licarete E, Florea F, Cristea V, Popescu O, Sitaru C, Chiriac MT. IgG antibodies against immunodominant C-terminal epitopes of BP230 do not induce skin blistering in mice. Human Immunology. 2014;**75**:354-363. DOI: 10.1016/j.humimm.2014.01.005

[38] Florea F, Koch M, Hashimoto T, Sitaru C. Autoimmunity against laminins. Clinical Immunology. 2016;**170**:39-52. DOI: 10.1016/j.clim.2016.07.021

[39] Has C, Spartà G, Kiritsi D, Weibel L, Moeller A, Vega-Warner V, Waters A, He Y, Anikster Y, Esser P, Straub BK, Hausser I, Bockenhauer D, Dekel B, Hildebrandt F, Bruckner-Tuderman L, Laube GF. Integrin α3 mutations with kidney, lung, and skin disease. The New England Journal of Medicine. 2012;**366**:1508-1514. DOI: 10.1056/NEJMoa1110813

[40] Sarrazin S, Lamanna WC, Esko JD. Heparan sulfate proteoglycans. Cold Spring Harbor Perspectives in Biology. 2011 Jul;**1**:3(7). DOI: 10.1101/cshperspect.a004952.10.1101/cshperspect.a004952

[41] Schmidt T, Hoch M, Lotfi Jad SS, Solimani F, Di Zenzo G, Marzano AV, Goebeler M, Cozzani E, Kern JS, Sitaru C, Lakoš Jukić I, Sárdy M, Uzun S, Jedlickova H, Gläser R, Kaneda M, Eming R, Göpel G, Ishii N, Greene B, Hashimoto T, Hertl M. Serological diagnostics in the detection of IgG autoantibodies against human collagen VII in epidermolysis bullosa acquisita - a multicenter analysis. The British Journal of Dermatology. 2017 Jul 13. DOI: 10.1111/bjd.15800

Chapter 2

Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment

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Additional information is available at the end of the chapter

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Abstract

Pemphigus is a group of autoimmune blistering disorders associated with autoantibodies against the keratinocyte cell surface. Pemphigus has three major variants: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP) which all have further subtypes. The variants of pemphigus are classified depending upon the clinical and histological features, immunofluorescence staining pattern, and autoantibody profile of the disease. The onset and course of pemphigus appear on the basis of interaction between genetic predisposition and various triggering factors. Pemphigus vulgaris is the most commonly seen and representative clinical form of pemphigus. Together with clinical manifestations, the histopathological and immunopathological data support the diagnosis. As though some pemphigus variants, particularly pemphigus vulgaris and paraneoplastic pemphigus, have a mortality risk, early diagnosis is necessary and onset of treatment should be promptly initiated. In this chapter, firstly, classification of pemphigus is described. After then, clinical features, histopathological and immunopathological findings, target antigens, etiopathogenesis and comorbidities of each pemphigus variant are discussed briefly.

Keywords: pemphigus, pemphigus variants, clinical manifestations, pathogenesis, histopathology, immunopathology

1. Introduction

Pemphigus is a distinct organ-specific autoimmune blistering disorder involving skin and mucous membranes associated with autoantibodies directed against desmosomes-intercellular adhesive molecule complex localized on the keratinocyte cell surface [1–4].

Pemphigus has three major variants, which are classified depending on the basis of the clinical, histological features, immunofluorescence staining pattern and autoantibody profile of the disease including **pemphigus vulgaris (PV)**, **pemphigus foliaceus (PF)**, and **paraneoplastic pemphigus (PNP)**, which all have further subtypes. Less frequently seen and newer variants of pemphigus include **IgA pemphigus (IGAP)** and **pemphigus herpetiformis (PH)** [1–6].

The term "pemphigus" origins from the Greek word "pemphix", which has a meaning of "blister" [1]. It is a chronic potentially life-threating bullous disorder if not treated on time [4, 7, 8]. The phenotypes of pemphigus represent a complex spectrum with multiple genetic and environmental factors playing a role in disease pathogenesis [9, 10].

Together with clinical manifestations, the histopathological and immunopathological data support the diagnosis of the disease. The best site for the cutaneous biopsy for the appropriate histopathological examination is a fresh (< 24 h) small vesicle or 1/3 of the peripheral portion of the blister including the perilesional normal appearing skin. For direct immunofluorescence microscopic (DIF) examination, a perilesional normal appearing skin area up to 1 cm from a fresh vesicle should be taken and should be transformed in saline or in a cylinder of liquid nitrogen in a period lesser than 36 h [11–13].

As though some pemphigus variants, particularly PV and PNP, are potentially life-threatening diseases, early diagnosis is necessary and early onset of immunosuppressive treatment should be promptly initiated [14]. Moreover, some variants of pemphigus may indicate the presence of an underlying malignancy [15].

In this chapter, after the classification of pemphigus, firstly, pathogenetic properties and mechanism of acantholysis are discussed. After then, the review of pemphigus including the epidemiology, clinical features, histopathological and immunopathological findings, target antigens, and comorbidities of each pemphigus variant is discussed briefly.

2. The classification of pemphigus

Pemphigus is classified into two major types according to the level of intraepidermal separation by the most authors: PV and PF [2, 16, 17]. In the last decades, rarer and newer variants of pemphigus have taken part in classification [1, 4, 6], which is described in the following sections.

3. Pathomechanism of pemphigus

The evidence outlines that pemphigus is mediated by pathogenic circulating anti-Desmoglein 1/3 (Dsg) antibodies, which mediate blister formation [1–6, 16–21]. Previously, it was accepted that the presence of anti-Dsg antibodies alone is sufficient for the development of pemphigus [22]. According to the compensation hypothesis, the development of pemphigus is based on the normal epidermal distribution of Dsg1 and 3 molecules and Dsg1 and 3 antibody profiles [2, 16]. However, several reports have been reported pointing the discrepancy between clinical phenotype and autoantibody profile that contradicts with this theory [22–26].

While the production of pathogenic autoantibodies (Abs) is the key for the development of the disease, today it is obvious that many immunological steps are also required prior to the antibody induction [3, 22, 27]. Recent studies investigating the role of lymphocytes have demonstrated the role of T cells and B cells in mouse models of pemphigus and patients, revealing insights into the mechanisms of autoimmunity [28].

Today, it is obvious that some HLA class II alleles are involved in the activation of Dsg3-specific CD4+ T cells, which drives the pathogenetic pathways. The epidermal loss of adhesion is induced by pathogenic IgG Abs, which are produced by B cells. HLA-DRB1*04:02 is highly prevalent in PV, which provides the recognition of Dsg3 by CD4+ T cells. T cell-dependent B cell activation is critical for the induction of pathogenic IgG Abs [28–31].

Recent studies have also emphasized the important role of T regulatory (reg) cells in the development of pemphigus, and it has been concluded that a balance between self-reactive lymphocytes and T reg cells may be a key element in determining whether individuals produce pathogenic Abs and develop pemphigus or not [9, 32, 33].

4. Pemphigus vulgaris

PV is the most commonly seen and representative clinical form of pemphigus with an incidence of 0.1–0.5/100.000 population [1, 2, 7, 13]. The average age at onset is usually at fourth and fifth decades, but may occur in the elderly or children. The incidence rate is higher among patients with Jewish and Mediterranean ancestry [1, 2, 5, 7, 13]. Various environmental factors such as drugs (captopril, penicillamine), infections (herpes simplex virus, Epstein–Barr virus, etc.), pesticides, ultraviolet radiation (UVR), ionizan radiation, thermal burns, stress and food containing an allium, phenol, thiol, or urushiol have been reported to trigger PV [10, 13, 34].

4.1. Clinical features

Patients with PV may present with only mucosal involvement and some with both mucosal and skin involvement [2, 4, 5]. In majority of the patients, oral mucosa is the site of onset, while cutaneous involvement usually occurs subsequently. It is most commonly characterized by painful erosions, erosions with whitish exudate and erythematous patches usually localized on gingiva and buccal mucosa [1, 2, 4, 5, 13] (**Figures 1** and **2**). The other mucosal areas, nasal cavity, larynx (epiglottis, vocal cords), oropharynx, esophagus, vagina, vulva, penis, and anus may also be affected [1, 13]. Epistaxis and hoarseness are present owing to the involvement of the nose, pharynx, and larynx [1, 13, 35–37]. Genital mucosa is one of the frequent sites involved in PV after the oral mucosa [37].

Cutaneous involvement usually follows mucosal lesions by 3 or 4 months [1, 4, 5]. The skin lesions cause burning and painful sensation. Cutaneous lesions are characterized by flaccid bullae evolving into painful extensive erosive areas (**Figure 3**). These blisters appear on the normal or erythematous skin, which are fragile, break rapidly, and it is hard to find an unruptured bullae. The Nikolsky sign is present. The bullae in PV can be localized or generalized, and any area

Figure 1. The eroded lesions are seen on the palate, right and left sides of the lower lip.

of the skin may be involved. The most frequent areas affected are: face, axilla, and scalp, and this may be due to the fact that Dsg3 has its highest expression in these areas [1, 2]. Umbilicus and/or nail involvement are the other sites that may be affected [2, 4, 5, 13, 38–40]. The presence of the nail lesions may be the sign of relapse or recurrence of the disease [40]. Apart from these, cases of PV with the involvement of only cutaneous lesions have also been reported [41–43].

4.2. Histopathology

Intraepidermal suprabasal acantholysis and infiltration with predominantly neutrophils and eosinophils are observed (tombstone pattern) [2, 5, 13].

4.3. Immunopathology and target antigens

DIF examination shows lace-like IgG deposition with or without C3 on the surface of the keratinocytes in the mid-lower or entire epidermis [2, 5, 12, 13, 16]. Indirect immunofluorescence

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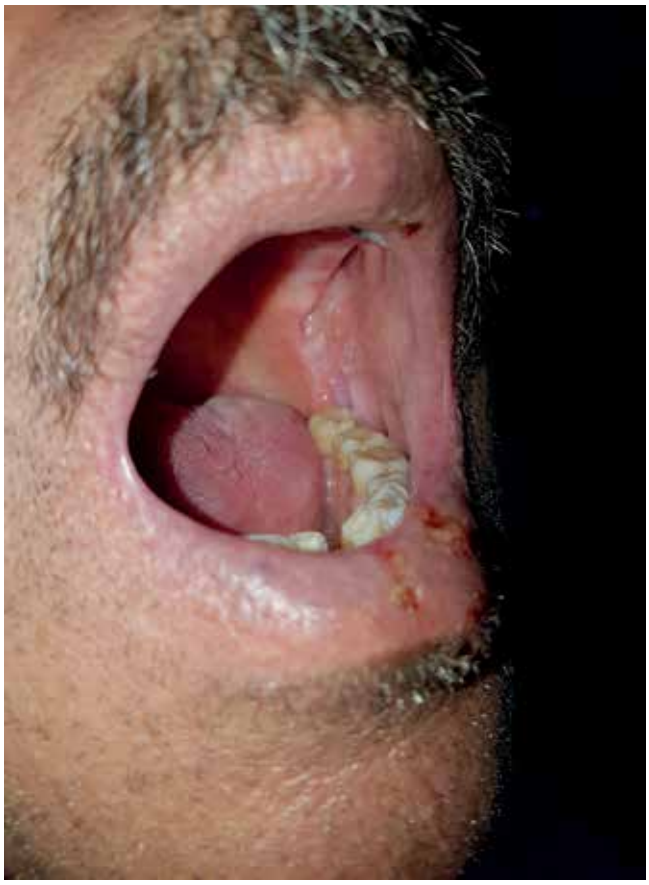

Figure 2. The erosions with whitish exudates are seen on the left posterior side of the buccal mucosa.

(IIF) examination, using a substrate of normal human skin or monkey esophagus, shows circulating antiepithelial IgG and lace-like deposition [2, 4, 5, 12]. Enzyme-linked immunosorbent assay (ELISA) is also available in detecting antigens of PV and serves as a tool for assessing the disease severity [44, 45]. Target antigens identified in PV are Dsg1 (with a molecular weight (MW) of 165 kD) and Dsg3 (MW-130 kD) [2–5, 9]. Desmocollin (Dcs) is another antigen that is thought to be responsible in some pemphigus patients [46, 47].

4.4. Associated diseases

Myasthenia gravis (MG) and abnormalities of thymus including benign or malignant thymoma and thymic hyperplasia have been reported to be associated with PV [2, 5, 48, 49]. Thymic abnormalities may precede or follow the onset of pemphigus. The other common disorders that have been reported to be associated with PV are systemic lupus erythematosus (SLE), bullous pemphigoid (BP), and PF [48].

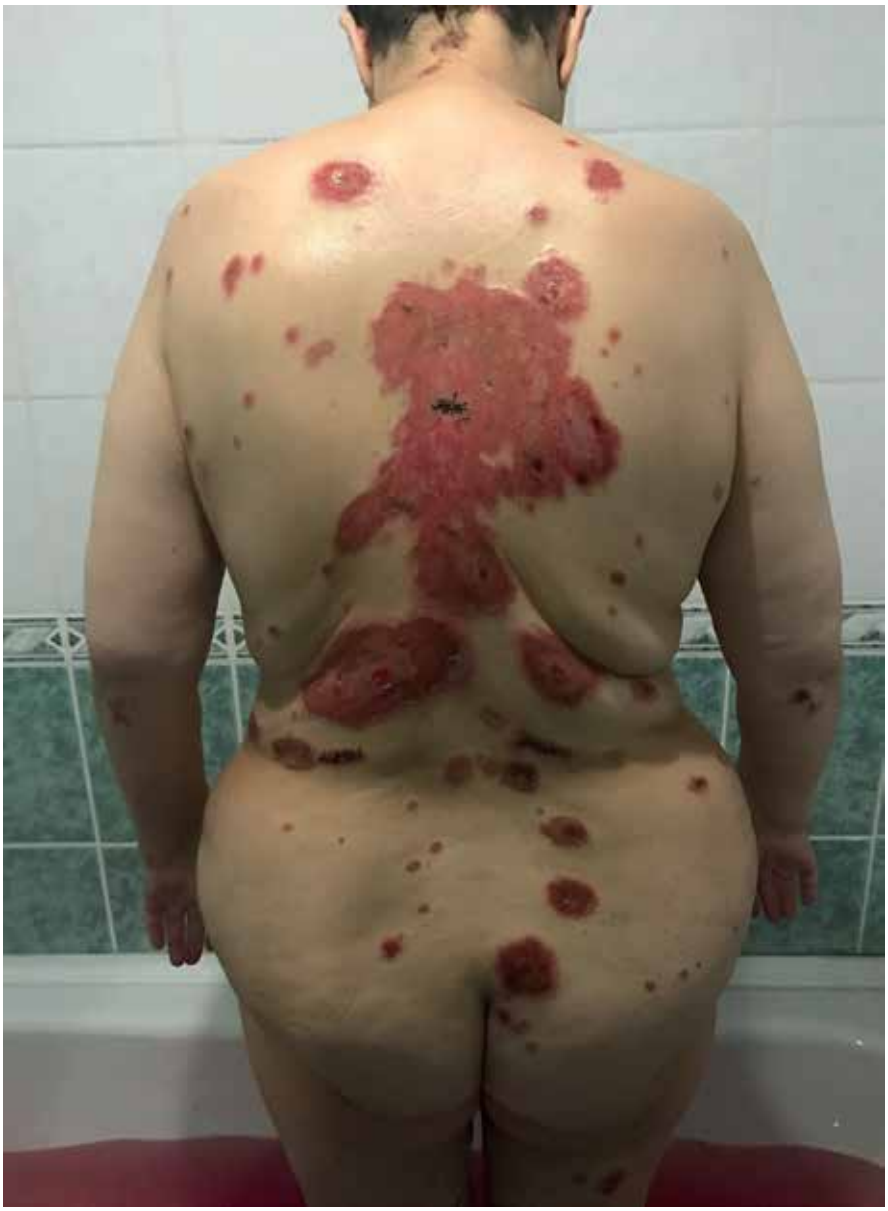

Figure 3. The extensive erosions localized on the back of the patient.

5. Pemphigus vegetans

Pemphigus vegetans (P veg) is accepted as the rarest variety of PV comprising of only 1–2% of all pemphigus patients. P veg has been reported to occur in all age groups, affecting primarily middle-aged females (sex ratio: F/M = 14/3) [50].

5.1. Clinical features

P veg is characterized by vegetative lesions preferentially affecting intertriginous (axillary, inframammarial areas) and periorificial regions [2, 5, 50–52]. The initial course of the disease is similar to PV. In the later stages, tumid vegetating, hypertrophic and verrucous lesions occur specifically between skin folds [5, 50, 53]. Two subtypes of P veg are recognized. The first one is Neumann P veg, which usually begins like PV with easily rupturing vesicles and bullae that evolve to form hypertrophic granulating erosions and then vegetating exuding masses. The second type is Hallopeau P veg, which is initially characterized by pustular lesions that break and gradually evolve into vegetating erosions [5, 50]. Mucosal involvement may not always be seen. Involvement of the vermillion border of the lips is the clinical hallmark of oral involvement [54]. Nail involvement is rarely described [50]. In P veg, the course of the disease is long, with remission and recurrence periods. Hallopeau P veg has a relatively benign course, while the Neumann type is often refractory to therapy. One of the frequent complications is the development of secondary bacterial infections, and also malnutrition and cachexia may coexist to the condition [5, 50].

5.2. Histopathology

Suprabasal acantholysis is present in the earlier stages of P veg similar to PV. In the following periods, irregular epidermal hyperplasia, papillomatosis, microabscess composed of eosinophils and neutrophils are also seen [2, 5, 50].

5.3. Immunopathology and target antigens

DIF and IIF examination results are indistinguishable from the findings of PV. As P veg is a subtype of PV, it is expected to react with the same antigens, Dsg1 and Dsg3 [2, 5, 50]. The presence of auto-Abs targeting additional desmosomal proteins including Dsc1, Dsc2, Dsc3 and periplakin have also been reported [51, 55].

5.4. Associated diseases

There are a few reports of P veg associated with internal malignancies and HIV infection [48, 50, 56, 57].

6. Pemphigus foliaceus

PF (foliaceus originates from the Latin word folium with a meaning of “leaf”) is the superficial form of pemphigus [1, 2, 4, 5]. PF has a universal occurrence and occurs sporadically, while the endemic form of PF, called as fogo selvagem (FS) or wild fire (WF), is predominantly seen in the rural and tropical regions of Brazil [5, 7, 16, 58, 59]. Another variant of PF, a localized form, is called as pemphigus erythematosus (PE) [16, 59]. Sporadic form of PF is most common in Europe and USA [16].The average age of PF ranges between 40 and 60 years, while FS is very often in children, adolescents and young adults. It is usually seen equally in both

females and males with a female preponderancy [59, 60]. FS occurs in genetically related family members. It has been reported that black fly (Simulium nigrimanum) bites were more frequent in patients with FS than in control patients [61, 62]. The authors suggested this vector or other infectious agents carry a molecule-triggering anti-Dsg1 response through antigen mimicry or cross-reactivity [58, 61].

6.1. Clinical features

PF is considered as a more benign form of the disease generally presenting with only cutaneous involvement [2, 5, 16, 59]. However, transition from PV to PF or vice versa may be observed [63–65]. More rarely, transition to BP has been reported [65]. The primary clinical feature of PF is fragile, superficial bullae evolving rapidly to erosive lesions. Nikolsky sign is positive. PF usually begins on the trunk, but may also be localized on the face and scalp. Sometimes yellowish crusted and scaly erythematous plaques on face and trunk predominate the clinical findings resembling the clinical picture of seborrheic dermatitis [2, 5, 16, 59, 66]. In FS, the disease usually begins on the head, neck, and seborrheic regions of the skin. The oral mucosa, palms of the hands, and plant of the feet are usually spared [59, 66]. In both PF and FS, lesions may become confluent and can transform to exfoliative erythroderma [67]. These patients should be hospitalized due to the risk of metabolic instability and mortality [1, 16, 59]. Pain and/or burning sensation may be noted. Unlike PV, there is no oral or other mucosal involvement [2, 5, 16, 59]. Mildest form of PF may be misdiagnosed for years [61].

6.2. Histopathology

Histological separation is more superficial than PV and exists along the granular layer. Eosinophilic spongiosis may also be seen in very early forms of PF [2, 5, 16, 59].

6.3. Immunopathology and target antigens

DIF and IIF examination findings are identical to the findings of PV [1, 5, 16, 59]. The intensity of the fluorescent stain is greater in the upper epidermis. Dsg1 is the specific target antigen [59].

6.4. Associated diseases

PF may be associated with MG and thymoma [2, 5, 16, 48]. A few cases of coexistence of PF with psoriasis [68, 69], malignancy [70, 71] and Graves' disease [72] have been reported. There also a few reports regarding cases of UVR and radiotherapy-induced PF [59, 73, 74].

7. Pemphigus erythematosus

PE, also known as Senear-Usher syndrome, is a localized form of PF [2, 5, 16, 59]. It affects most frequently elderly population. Clinical and immunological features of PE resemble both PF and cutaneous lupus erythematosus (LE) [16, 75]. Clinically erythematous plaques, scaly

to crusted lesions, occur across the malar areas of the face in a butterfly distribution mimicking the clinical appearance of LE [16]. The lesions are usually induced by UVR [75]. In 80% of the patients, antinuclear antibodies (ANA) without the presence of anti-ds-DNA antibodies may be detected [1, 2, 5, 16, 59]. DIF examination of the lesions may show both intercellular (IC) deposition IgG/C3 and granular deposition of IgG and C3 at the dermoepidermal junction (lupus band test) [5, 16, 59, 75].

8. Paraneoplastic pemphigus

PNP is a rare disease that manifests with clinically distinct painful mucosal erosions and polymorphic cutaneous lesions [1, 4, 15, 76]. The incidence of PNP is thought to be less common than PV or PF. PNP presents most often in older patients aged between 45 and 70 years [77, 78]. In almost all cases, PNP is associated with neoplasms mostly with lymphoproliferative diseases [4, 15, 66, 76–78].

8.1. Clinical features

The onset of the lesions usually presents with initially limited cheilitis and/or ulcerative stomatitis, which then progresses to severe, intractable, hemorrhagical stomatitis with persistent painful mucosal ulcerations in the oropharynx and esophagus [4, 5, 15, 16, 77]. Oral lesions usually extend to the vermillion border of the lips [15, 77]. Eye involvement especially includes conjunctival erosions and occurs in 70% of patients [79–82]. Cutaneous lesions are usually seen after the onset of mucosal involvement with a duration of days to months [77, 83, 84]. Cutaneous lesions are widespread and are usually polymorphic including lichenoid lesions, erythema multiforme-like lesions, vesiculobullous and erosive lesions. The palmar involvement is usually observed [4]. Lichen planus-like lesions localized on skin, nails and/or mucosa resemble lichen planus, target-like lesions resemble erythema multiforme, and bullous lesions and erosive lesions resemble PV and bullous pemphigoid [4, 15, 66, 76, 77, 83–87]. Cutaneous lesions mimicking graft versus host disease or Stevens-Johnson syndrome may also be observed [86, 87].

As though most of the patients with PNP are associated with malignancies, the prognosis of PNP is severe with a high mortality rate [15, 77, 83, 84, 88, 89]. Internal organ involvement including lungs (Bronchiolitis obliterans), thyroid, kidney and gastrointestinal system has been documented [15, 88, 89]. Most authors have reported that the term "paraneoplastic pemphigus" is too restrictive to describe the developing multiorgan syndrome involvement and have suggested a new nomenclature named as paraneoplastic autoimmune multiorgan syndrome (PAMS) [15, 88].

8.2. Histopathology

Several biopsies are often required to achieve the diagnosis [77, 81]. The histopathological features of PNP reveal variability according to the type of the morphology of the cutaneous

lesion [15, 77, 84, 90]. Intraepidermal suprabasal acantholysis (resembling PV), keratinocyte necrosis and vacuolar interface changes (resembling erythema multiforme/lichen planus) may be observed [77, 90].

8.3. Immunopathology and target antigens

DIF examination is characterized by the deposition of immunoreactants (IgG deposits with or without compleman) in IC region of epidermis and deposition of IgG/IgM and/or C3 along the basal zone membrane (BZM) [15, 17, 77, 84]. IIF using rat bladder epithelium as substrate shows an IC pattern that appears to be highly specific but less sensitive for PNP/PAMPS (including monkey esophagus (86% sensitivity) and murine tongue (100% sensitivity). A variety of antigens including Dsg1, Dsg3, envoplakin, periplakin, bullous pemphigoid antigen1 (BPAG1), plectin, desmoplakin 1, and desmoplakin 2 can be detected by immunoprecipitation [15, 17, 77, 84].

8.4. Associated diseases

PNP usually precedes the diagnosis of the underlying malignancy. In 1/3 of the cases, the underlying malignancy has not been diagnosed at the time of diagnosis. Therefore, when a diagnosis of PNP is made, a comprehensive workup for an underlying malignancy is mandatory [4, 15, 76, 77]. Hematological malignancies are associated with 84% of the patients of PNP. The most common reported hematological malignancies are non-Hodgkin lymphoma (38.6%), chronic lymphocytic leukemia (18.4%), Castleman disease (18.4%), and thymoma (5.5%) [15, 48, 77, 84].

9. Pemphigus herpetiformis

PH is a rare and distinct entity of pemhigus [6, 11]. It has been first described in patients who had clinical features that resemble dermatitis herpetiformis, but showed the features of pemphigus histopathologically and immunologically [6, 11, 91, 92]. It usually accounts 6–7% of cases and affects females and males equally [11, 92].

9.1. Clinical features

Patients usually have erythematous, gyrate, annular and polycyclic lesions with clusters of pustules, vesicles, in herpetiform pattern. The clinical presentation of PH may be atypical and may mimic various other bullous diseases [6, 92]. Pruritus is usually present [6, 11, 92, 93]. Mucous involvement is not a usual finding [6, 11]. PH usually has a good psis, although some cases may progress into classic pemphigus [11, 94].

9.2. Histopathology

The histopathological examination shows eosinophilic or neutrophilic spongiosis and microabscesses (neutrophils and/or eosinophils) in the mid or subcorneal epidermis mostly without acantholysis. Acantholysis may be seen in the later stages of the disease process and may be minimal [6, 11, 92, 93].

9.3. Immunopathology and target antigens

DIF examination shows IC deposits of IgG and C3 in epidermis, while IIF examination shows circulating IgG auto-Abs. The target antigen is usually Dsg 1 (or less frequently Dsg3) [6, 11, 95]. Recent studies have demonstrated DSc1, Dsc3 and unknown protein 178-kDa protein [11, 92, 96] by immunoblotting.

9.4. Associated diseases

There is evidence of association of PH with some diseases such as SLE, autoimmune hemolytic anemia and psoriasis and with some malignancies (prostate, esophagus) in the literature [11, 97–101].

10. IgA pemphigus

IGAP is a rare entity of pemphigus [6, 11]. It has two clinical types: intraepidermal neutrophilic type (IEN) and subcorneal pustular dermatosis (SPD) [6, 11, 66]. It is usually observed in the middle-aged or the elderly with an average age at 48 years, but also has been reported in childhood [6, 11]. There is a slight predominance of females [6].

10.1. Clinical features

Patients with both types of IGAP present with flaccid vesicles or pustules on either erythematous or normal skin mostly localized on axillary and groin areas, but trunk, proximal extremities and abdominal regions are also involved. The pustules tend to coalesce to form annular or circinate pattern. SPD is clinically indistinguishable from the disease subcorneal pustular dermatosis. In IEN type, pustules coalesce to form a sunflower-like configuration [2, 6, 11, 102, 103]. Pruritus is severe and affects patients' daily activities. Mucosal involvement is rare [2, 6, 11].

10.2. Histopathology

There is slight acantholysis and neutrophilic infiltration in epidermis. In SPD type, neutrophilic infiltration is localized subcorneally in the upper epidermis, while in IEN type in lower epidermis or entire epidermis [5, 6, 11].

10.3. Immunopathology and target antigens

In DIF examination, deposition of IgA in IC space of epidermis is detected. IgG and/or C3 is sometimes deposited but is weaker than IgA. In the SPD type, deposition is limited to upper epidermis, while in IEN type, it is deposited in lower epidermis or in whole epidermis [6, 11]. Using healthy human skin and monkey esophagus, circulating IgA auto-Abs have been demonstrated in 50% of the patients [5, 11]. The antigens in IGAP are Dsg1, Dsg3, Dsc1, and Dsc3 [3, 4]

10.4. Associated diseases

In SPD type, the most frequently reported association is monoclonal IgA gammopathy [11, 48, 103]. **The skin symptoms may precede monoclonal IgA or may be detected during the disease course** [104]**. The other associated diseases are** multiple myeloma, lymphoma, Crohn disease, and ulcerative colitis [48, 103, 104].

11. Conclusion

Pemphigus, especially some types, is a life-threatening disease and has a mortality risk. Therefore, the diagnosis should be made as soon as possible, and the treatment should be started. Today, a better understanding of the role of immunological dysregulation in the pathogenesis will also cause offering newly targeted therapeutical agents in the treatment of pemphigus.

Abbreviations

Abs	Antibodies
ACE	Angiotensin-converting enzyme
ANA	Antinuclear antibody
Anti-ds DNA	Double-stranded DNA antibody
BO	Bronchiolitis obliterans
BZM	Bazal zone membrane
C3	Compleman 3
DIF	Direct immunofluorescence
Dsc	Desmocollin
Dsg	Desmoglein
ELISA	Enzyme-linked immunosorbent assay
FS	FogoSelvagem
HLA	Human leucocyte antigen
IC	Intercellular
IEN	Intraepidermal neutrophilic type
Ig	Immunoglobulin

IGAP	IgA Pemphigus
IIF	Indirect immunofluorescence
MG	Myasthenia gravis
MW	Molecular weight
P veg	Pemphigus vegetans
PAMPS	Paraneoplastic autoimmune multi-organ syndrome
PE	Pemphigus erythematosus
PF	Pemphigus foliaceus
PH	Pemphigus herpetiformis
PNP	Paraneoplastic pemphigus
PV	Pemphigus vulgaris
Reg	Regulatory
SLE	Systemic lupus erythematosus
UVR	Ultraviolet radiation
WF	Wild fire

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References

[1] Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. Autoimmunity Reviews. 2014;**13**:482-489. DOI: 10.1016/j.autrev.2014.01.047

[2] Amagai M. Pemphigus. In: Bolognia JL, Jorizzo JL, Schaffer JV, Bolognia JL, editors. Dermatology. 2nd edt. Vol. 1. Ch. 29. China: Elsevier Saunders. 2012;461-474

[3] Kitajima Y, Aoyama Y. A perspective of pemphigus from bedside and laboratory – bench. Clinical Reviews in Allergy and Immunology. 2007;**33**:57-66. DOI: 10.1007/s12016-007-0036-5

[4] Hertl M, Jedlickova H, Karpati S, et al. Pemphigus. S2 guideline for diagnosis and treatment--guided by the European dermatology forum (EDF) in cooperation with the European academy of dermatology and venereology (EADV). Journal of the European Academy of Dermatology and Venereology. 2015;**29**:405-414. DOI: 10.1111/jdv.12772

[5] Stanley JR. In: Wolff K, Goldsmith LA, Katz SI, et al., editors. Fitzpatrick's Dermatology in General Medicine. Vol 1. Ch 52. 7th ed. New York: McGraw Hill; 2008. pp. 459-468

[6] Robinson ND, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. Journal of the American Academy of Dermatology. 1999;**40**:649-671; quiz 672-3. PMID: 10321591

[7] Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: Pemphigus and bullous pemphigoid. Archives of Dermatological Research. 2015;**307**:291-298. DOI: 10.1007/s00403-014-1531-1

[8] Huang YH, Kuo CF, Chen YH, Yang YW. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: A nationwide population-based study. The Journal of Investigative Dermatology. 2012;**132**:92-97. DOI: 10.1038/jid.2011.249

[9] Di Zenzo G, Amber KT, Sayar BS, Müller EJ, Borradori L. Immune response in pemphigus and beyond: Progresses and emerging concepts. Seminars in Immunopathology. 2016;**38**:57-74. DOI: 10.1007/s00281-015-0541-1

[10] Ruocco V, Ruocco E, Lo Schiavo A, et al. Pemphigus: Etiology, pathogenesis, and inducing or triggering factors: Facts and controversies. Clinics in Dermatology. 2013;**31**:374-381. DOI: 10.1016/j.clindermatol.2013.01.004

[11] Porro AM, Caetano Lde V, Maehara Lde S, Enokihara MM. Non-classical forms of pemphigus: Pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. Anais Brasileiros de Dermatologia. 2014;**89**:96-106. DOI: 10.1590/abd1806-4841.20142459

[12] Pohla-Gubo G, Hintner H. Direct and indirect immunofluorescence for the diagnosis of bullous autoimmune diseases. Dermatologic Clinics. 2011;**29**:365-372, vii. DOI: 10.1016/j.det.2011.03.001

[13] Venugopal SS, Murrell DF. Diagnosis and clinical features of pemphigus vulgaris. Dermatologic Clinics. 2011;**29**:373-380, vii. DOI: 10.1016/j.det.2011.03.004

[14] Kridin K, Sagi SZ, Bergman R. Mortality and cause of death in patients with pemphigus. Acta Dermato-Venereologica. 2017 8;**97**:607-611. DOI: 10.2340/00015555-2611

[15] Kartan S, Shi VY, Clark AK, Chan LS. Paraneoplastic pemphigus and autoimmune blistering diseases associated with neoplasm: Characteristics, diagnosis, associated neoplasms, proposed pathogenesis, treatment. American Journal of Clinical Dermatology. 2017;**18**:105-126. DOI: 10.1007/s40257-016-0235-z

[16] Bystryn JC, Rudolph JL. Pemphigus. Lancet. 2005;**366**:61-73. DOI: 10.1016/S0140-6736(05)66829-8

[17] Kershenovich R, Hodak E, Mimouni D. Diagnosis and classification of pemphigus and bullous pemphigoid. Autoimmunity Reviews. 2014;**13**:477-481. DOI: 10.1016/j.autrev.2014.01.011

[18] Amagai M. Desmoglein as a target in autoimmunity and infection. Journal of the American Academy of Dermatology. 2003;**48**:244-252. DOI: 10.1067/mjd.2003.7

[19] Waschke J. The desmosome and pemphigus. Histochemistry and Cell Biology. **130**:21-54. DOI: 10.1007/s00418-008-0420-0

[20] Kitajima Y. 150(th) anniversary series: Desmosomes and autoimmune disease, perspective of dynamic desmosome remodeling and its impairments in pemphigus. Cell Communication & Adhesion. 2014;**21**:269-280. DOI: 10.3109/15419061.2014.943397

[21] Kitajima Y. New insights into desmosome regulation and pemphigus blistering as a desmosome-remodeling disease. The Kaohsiung Journal of Medical Sciences. 2013;**29**:1-13. DOI: 10.1016/j.kjms.2012.08.001

[22] Amagai M, Ahmed AR, Kitajima Y, et al. Are desmoglein autoantibodies essential for the immunopathogenesis of pemphigus vulgaris, or just witnesses of disease. Experimental Dermatology. 2006;**15**:815-831. DOI: 10.1111/j.1600-0625.2006.00499_1.x

[23] Carew B, Wagner G. Cutaneous pemphigus vulgaris with absence of desmoglein 1 autoantibodies. An example of the extended desmoglein compensation theory. The Australasian Journal of Dermatology. 2014;**55**:292-295. DOI: 10.1111/ajd.12154

[24] Cozzani E, Di Zenzo G, Riva S, et al. Are clinical phenotype and autoantibody profile always concordant in pemphigus? A study in a cohort of pemphigus patients. European Journal of Dermatology. 2013;**23**:40-48. DOI: 10.1684/ejd.2012.1903

[25] Ahmed AR, Carrozzo M, Caux F, et al. Monopathogenic vs multipathogenic explanations of pemphigus pathophysiology. Experimental Dermatology. 2016;**25**:839-846. DOI: 10.1111/exd.13106

[26] Saruta H, Ishii N, Teye K, et al. Two cases of pemphigus vegetans with IgG anti-desmocollin 3 antibodies. JAMA Dermatology. 2013;**1**(49):1209-1213. DOI: 10.1001/jamadermatol.2013.5244

[27] Amber KT, Staropoli P, Shiman MI, et al. Autoreactive T cells in the immune pathogenesis of pemphigus vulgaris. Experimental Dermatology. 2013;**22**:699-704. DOI: 10.1111/exd.12229

[28] Giordano CN, Sinha AA. Cytokine networks in pemphigus vulgaris: An integrated viewpoint. Autoimmunity. 2012;**45**:427-439. DOI: 10.3109/08916934.2012.697593

[29] Eming R, Hennerici T, Bäcklund J, et al. Pathogenic IgG antibodies against desmoglein 3 in pemphigus vulgaris are regulated by HLA-DRB1*04:02-restricted T cells. Journal of Immunology. 2014;**193**(9):4391. DOI: 10.4049/jimmunol.1401081

[30] Yan L, Wang JM, Zeng K. Association between HLA-DRB1 polymorphisms and pemphigus vulgaris: A meta-analysis. The Journal of Dermatology. **167**(4):768-777. DOI: 10.1111/j.1365-2133.2012.11040.x

[31] Hertl M, Riechers R. Analysis of the T cells that are potentially involved in autoantibody production in pemphigus vulgaris. The Journal of Dermatology. 1999;**26**:748-752 10635617

[32] Schmidt T, Willenborg S, Hünig T, et al. Induction of T regulatory cells by the superagonistic anti-CD28 antibody D665 leads to decreased pathogenic IgG autoantibodies against desmoglein 3 in a HLA-transgenic mouse model of pemphigus vulgaris. Experimental Dermatology. 2016;**25**:293-298. DOI: 10.1111/exd.12919

[33] Yokoyama T, Amagai M. Immune dysregulation of pemphigus in humans and mice. The Journal of Dermatology. 2010;**37**:205-213. DOI: 10.1111/j.1346-8138.2009.00797.x

[34] Brenner S, Goldberg I. Drug-induced pemphigus. Clinics in Dermatology. 2011;**29**:455-457. DOI: 10.1016/j.clindermatol.2011.01.016

[35] Robati RM, Rahmati-Roodsari M, Dabir-Moghaddam P, et al. Mucosal manifestations of pemphigus vulgaris in ear, nose, and throat; before and after treatment. Journal of the American Academy of Dermatology. 2012;**67**:e249-e252. DOI: 10.1016/j.jaad.2011.06.022

[36] Fernandez S, Espana A, Navedo M, Barona L. Study of oral, ear, nose and throat involvement in pemphigus vulgaris by endoscopic examination. The British Journal of Dermatology. 2012;**167**:1011-1016. DOI: 10.1111/j.1365-2133.2012.11098.x

[37] Akhyani M, Chams-Davatchi C, Naraghi Z, et al. Cervicovaginal involvement in pemphigus vulgaris: A clinical study of 77 cases. The British Journal of Dermatology. 2008;**158**:478-482. DOI: 10.1111/j.1365-2133.2007.08356.x

[38] Oliveira Júnior JV, Maruta CW, Sousa JX Jr, et al. Clinical and immunological profile of umbilical involvement in pemphigus vulgaris and pemphigus foliaceus. Clinical and Experimental Dermatology 2013;**38**:20-24. DOI: 10.1111/j.1365-2230.2012.04468.x.

[39] Carducci M, Calcaterra R, Franco G, et al. Nail involvement in pemphigus vulgaris. Acta Dermato-Venereologica. 2008;**88**:58-60. DOI: 10.2340/00015555-0255

[40] Tosti A, André M, Murrell DF. Nail involvement in autoimmune bullous disorders. Dermatologic Clinics. 2011;**29**(3):511-513, xi. DOI: 10.1016/j.det.2011.03.006

[41] Yoshida K, Takae Y, Saito H, et al. Cutaneous type pemphigus vulgaris: A rare clinical phenotype of pemphigus. Journal of the American Academy of Dermatology. 2005;**52**:839-845. DOI: 10.1016/j.jaad.2005.01.106

[42] Shinkuma S, Nishie W, Shibaki A, et al. Cutaneous pemphigus vulgaris with skin features similar to the classic mucocutaneous type: A case report and review of the literature. Clinical and Experimental Dermatology. 2008;**33**:724-728. DOI: 10.1111/j.1365-2230.2008.02871.x

[43] Nagasaka A, Matsue H, Miyahara A, Shimada S. Pemphigus vulgaris with no mucosal lesions showing pemphigus-foliaceus-like skin manifestations: Is there a 'cutaneous type' of pemphigus vulgaris? Dermatology. 2005;**211**(4):372. DOI: 10.1159/000088513

[44] Daneshpazhooh M, Chams-Davatchi C, Khamesipour A, et al. Desmoglein 1 and 3 enzyme-linked immunosorbent assay in Iranian patients with pemphigus vulgaris: Correlation with phenotype, severity, and disease activity. Journal of the European Academy of Dermatology and Venereology. 2007;**21**(10):1319-1324. DOI: 10.1111/j.1468-3083.2007.02254.x

[45] Barnadas MA, Rubiales MV, Gich I, Gelpí C. Usefulness of specific anti-desmoglein 1 and 3 enzyme-linked immunoassay and indirect immunofluorescence in the evaluation of pemphigus activity. International Journal of Dermatology. 2015;**54**:1261-1268. DOI: 10.1111/ijd.12768

[46] Mao X, Nagler AR, Farber SA, et al. Autoimmunity to desmocollin 3 in pemphigus vulgaris. The American Journal of Pathology. 2010;**177**:2724-2730. DOI: 10.2353/ajpath.2010.100483

[47] Kamiya K, Aoyama Y, Wakashima C, et al. Atypical pemphigus with immunoglobulin G autoantibodies against desmoglein 3 and desmocollin 3. The Journal of Dermatology. 2016;**43**:429-431. DOI: 10.1111/1346-8138.13086

[48] Ljubojevic S, Lpozencic J. Autoimmune bullous diseases associations. Clinics in Dermatology. 2012;**30**:17-33. DOI: 10.1016/j.clindermatol.2011.03.006

[49] Meyer S, Kroiss M, Landthaler M, Vogt T. Thymoma, myasthenia gravis, eruptions of pemphigus vulgaris and a favourable course of relapsing melanoma: An immunological puzzle. The British Journal of Dermatology. 2006;**155**:638-640. DOI: 10.1111/j.1365-2133.2006.07384.x

[50] Ruocco V, Ruocco E, Caccavale S, Gambardella A, Lo Schiavo A. Pemphigus vegetans of the folds (intertriginous areas). Clinics in Dermatology. 2015;**33**:471-476. DOI: 10.1016/j.clindermatol.2015.04.011

[51] Mergler R, Kerstan A, Schmidt E, Goebeler M, Benoit S. Atypical clinical and serological manifestation of pemphigus Vegetans: A case report and review of the literature. Case Reports in Dermatology. 2017;**9**:121-130. DOI: 10.1159/000468919

[52] Mori M, Mariotti G, Grandi V, Gunnella S, Maio V. Pemphigus vegetans of the scalp. Journal of the European Academy of Dermatology and Venereology. 2016;**30**:368-370. DOI: 10.1111/jdv.12793

[53] de Almeida HL Jr, Neugebauer MG, Guarenti IM, Aoki V. Pemphigus vegetans associated with verrucous lesions: Expanding a phenotype. Clinics (São Paulo, Brazil) 2006;**61**:279-282. DOI: /S1807-59322006000300016

[54] Mendes-Bastos P, Amaro C, Fernandes C. Cobblestone mouth: An exuberant oral presentation of pemphigus vegetans. Actas Dermo-Sifiliográficas. 2015;**106**:72-73. DOI: 10.1016/j.ad.2014.05.004

[55] Saruta H, Ishii N, Teye K, et al. Two cases of pemphigus vegetans with IgG anti-desmocollin 3 antibodies. JAMA Dermatology. 2013;**149**:1209-1213. DOI: 10.1001/jamadermatol.2013.5244

[56] Lateef A, Packles MR, White SM, Don PC, Weinberg JM. Pemphigus vegetans in association with human immunodeficiency virus. International Journal of Dermatology. 1999;**38**:778-781

[57] Torres T, Ferreira M, Sanches M, Selores M. Pemphigus vegetans in a patient with colonic cancer. Indian Journal of Dermatology, Venereology and Leprology. 2009;**75**:603-605. DOI: 10.4103/0378-6323.57724

[58] Aoki V, Rivitti EA, Diaz LA. The cooperative group on Fogo Selvagem research. Update on fogo selvagem, an endemic form of pemphigus foliaceus. The Journal of Dermatology. 2015;**42**:18-26. DOI: 10.1111/1346-8138.12675

[59] James KA, Culton DA, Diaz LA. Diagnosis and clinical features of pemphigus foliaceus. Dermatologic Clinics. 2011;**29**:405-412. DOI: 10.1016/j.det.2011.03.012

[60] Zaraa I, Mokni M, Hsairi M, et al. Pemphigus vulgaris and pemphigus foliaceus: Similar prognosis? International Journal of Dermatology. 2007;**46**:923-926. DOI: 10.1111/j.1365-4632.2007.03103.x

[61] Lombardi C, Borges PC, Chaul A, et al. Environmental risk factors in endemic pemphigus foliaceus (Fogo selvagem). "The cooperative group on Fogo Selvagem research". The Journal of Investigative Dermatology. 1992;**98**:847-850. PMID: 1593148

[62] Sampaio SA, Rivitti EA, Aoki V, Diaz LA. Brazilian pemphigus foliaceus, endemic pemphigus foliaceus, or fogo selvage (wild fire). Dermatologic Clinics. 1994;**12**:765-776. PMID: 7805306

[63] Kawana S, Hashimato T, Nishikawa T, Nishiyama S. Changes in clinical features, histologic findings, and antigen profiles with development of pemphigus foliaceus from pemphigus vulgaris. Archives of Dermatology. 1994;**130**:1534-1538. PMID: 7986127

[64] Tsuji Y, Kawashima T, Yokota K, et al. Clinical and serological transition from pemphigus vulgaris to pemphigus foliaceus demonstrated by desmoglein ELISA system. Archives of Dermatology. 2002;**138**:95-96. PMID: 11790172

[65] Recke A, Rose C, Schmidt E, et al. Transition from pemphigus foliaceus to bullous pemphigoid: Intermolecular B-cell epitope spreading without IgG subclass shifting. Journal of the American Academy of Dermatology. 2009;**61**:333-336. DOI: 10.1016/j.jaad.2008.10.061

[66] Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 1: Clinical manifestations. Journal der Deutschen Dermatologischen Gesellschaft. 2011;**9**:844-857. DOI: 10.1111/j.1610-0387.2011.07793.x

[67] Kunte C, Barbosa JM, Wolff H, Meurer M. Brazilian pemphigus foliaceus (fogo selvagem) [article in German]. Hautarzt. 1997;**48**:228-233. PMID: 9206709

[68] Tomasini D, Cerri A, Cozzani E, Berti E. Development of pemphigus foliaceus in a patient with psoriasis: A simple coincidence? European Journal of Dermatology. 1998;**8**:56-59. PMID: 9649683

[69] Panzarella K, Camisa C. Coexistence of superficial pemphigus and psoriasis. Cutis. 1996;**57**:414-418. PMID: 8804843

[70] Inaoki M, Kaji K, Furuse S, et al. Pemphigus foliaceus developing after metastasis of cutaneous squamous cell carcinoma to regional lymph nodes. Journal of the American Academy of Dermatology. 2001;**45**:767-770. DOI: 10.1067/mjd.2001.117398

[71] Ota M, Sato-Matsumara KC, Matsumara T, et al. Pemphigus foliaceus and figurate erythema in a patient with prostate cancer. The British Journal of Dermatology. 2000;**142**:816-818. PMID: 10792242

[72] Levine L, Benstein JE, Soltani K, et al. Coexisting childhood pemphigus foliaceus and graves' disease. Archives of Dermatology. 1982;**118**:602-604. PMID: 6896623

[73] Ambay A, Stratman E. Ionizing radiation-induced pemphigus foliaceus. Journal of the American Academy of Dermatology. 2006;**54**:251-252. DOI: 10.1016/j.jaad.2005.12.024

[74] Cianchini G, Lembo L, Colonna L, et al. Pemphigus foliaceus induced by radiotherapy and responsive to dapsone. The Journal of Dermatological Treatment. 2006;**17**:244-246. DOI: 10.1080/09546630600921197

[75] Makino T, Seki Y, Hara H, et al. Induction of skin lesions by ultraviolet B irradiation in a case of pemphigus erythematosus. Acta Dermato-Venereologica. 2014;**94**:487-488. DOI: 10.2340/00015555-1781

[76] Chorzelski T, Hashimoto T, Maciejewska B, et al. Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis and bronchiolitis obliterans. Journal of the American Academy of Dermatology. 1999;**41**:393-400. PMID: 10459112

[77] Tirado-Sánchez A, Bonifaz A. Paraneoplastic pemphigus. A life-threatening autoimmune blistering disease. Actas Dermo-Sifiliográficas. 2017 Aug 8. pii: S0001-7310(17)30370-8. DOI: 10.1016/j.ad.2017.04.024 [Epub ahead of print]

[78] Anhalt GJ. Paraneoplastic pemphigus: The role of tumours and drugs. The British Journal of Dermatology. 2001;**144**:1102-1104. PMID: 11422027

[79] Broussard KC, Leung TG, Moradi A, Thorne JE, Fine JD. Autoimmune bullous diseases with skin and eye involvement: Cicatricial pemphigoid, pemphigus vulgaris, and pemphigus paraneoplastica. Clinics in Dermatology. 2016;**34**:205-213. DOI: 10.1016/j.clindermatol.2015.11.006

[80] Meyers SJ, Varley GA, Meisler DM, Camisa C, Wander AH. Conjunctival involvement in paraneoplastic pemphigus. American Journal of Ophthalmology. 1992;**114**:621-624. PMID: 1443026

[81] Gong H, Zhou S, Hu Y, et al. Recurrent corneal melting in the paraneoplastic pemphigus associated with Castleman's disease. BMC Ophthalmology. 2016;**16**:106. DOI: 10.1186/s12886-016-0280-7

[82] Ahuero AE, Jakobiec FA, Bhat P, Ciralsky JB, Papaliodis GN. Paraneoplastic conjunctival cicatrization: Two different pathogenic types. Ophthalmology. 2010;**117**:659-664. DOI: 10.1016/j.ophtha.2009.09.006

[83] Frew JW, Murrell DF. Current management strategies in paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome). Dermatologic Clinics. 2011;**29**:607-612. DOI: 10.1016/j.det.2011.06.016

[84] Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. International Journal of Dermatology. 2011;**50**:905-914. DOI: 10.1111/j.1365-4632.2011.04868.x

[85] Mahler V, Antoni C, Anhalt GJ, et al. Graft-versus-host-like mucocutaneous eruptions with serological features of paraneoplastic pemphigus and systemic lupus erythematosus in a patient with non-Hodgkin's lymphoma. Dermatology. 1998;**197**:78-83

[86] Hayanga AJ, Lee TM, Pannucci CJ, et al. Paraneoplastic pemphigus in a burn intensive care unit: Case report and review of the literature. Journal of Burn Care & Research. 2010;**31**:826-829. DOI: 10.1097/BCR.0b013e3181eed4b4

[87] Yamada T, Nakamura S, Demitsu T, Nakamura T, Iida E, Yoneda K, Fukuda S, Hashimoto T. Paraneoplastic pemphigus mimicking toxic epidermal necrolysis associated with B-cell lymphoma. The Journal of Dermatology. 2013;**40**:286-288. DOI: 10.1111/1346-8138.12083

[88] Billet SE, Grando SA, Pittelkow MR. Paraneoplastic autoimmune multiorgan syndrome: Review of the literature and support for a cytotoxic role in pathogenesis. Autoimmunity. 2006;**39**:617-630. DOI: 10.1080/08916930600972099

[89] Namba C, Tohyama M, Hanakawa Y, Murakami M, Shirakata Y, Matsumoto T, Suemori K, Ishii N, Hashimoto T, Sayama K. Paraneoplastic pemphigus associated with fatal bronchiolitis obliterans and intractable mucosal erosions: Treatment with cyclosporine in addition to steroid, rituximab and intravenous immunoglobulin. The Journal of Dermatology. 2016;**43**:419-422. DOI: 10.1111/1346-8138.13160

[90] Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. Archives of Dermatology. 1992;**128**:1091-1095

[91] Maciejowska E, Jablonska S, Chorzelski T. Is pemphigus herpetiformis an entity? International Journal of Dermatology. 1987;**26**:571-577

[92] Kasperkiewicz M, Kowalewski C, Jabłońska S. Pemphigus herpetiformis: From first description until now. Journal of the American Academy of Dermatology. 2014;**70**:780-787. DOI: 10.1016/j.jaad.2013.11.043

[93] Laws PM, Heelan K, Al-Mohammedi F, Walsh S, Shear NH. Pemphigus herpetiformis: A case series and review of the literature. International Journal of Dermatology. 2015;**54**:1014-1022. DOI: 10.1111/ijd.12582

[94] Muramatsu T, Iida T, Honoki K, et al. Pemphigus vulgaris preceded by herpetiform-like skin lesions with negative immunofluorescence findings. The Journal of Dermatology. 1999;**26**:154-159. PMID: 10209921

[95] Lebeau S, Müller R, Masouyé I, Hertl M, Borradori L. Pemphigus herpetiformis: Analysis of the autoantibody profile during the disease course with changes in the clinical phenotype. Clinical and Experimental Dermatology. 2010;**35**:366-372. DOI: 10.1111/j.1365-2230.2009.03525.x

[96] Tateishi C, Tsuruta D, Nakanishi T, et al. Antidesmocollin-1 antibody-positive, antidesmoglein antibody-negative pemphigus herpetiformis. Journal of the American Academy of Dermatology. 2010;**63**:e8-10. DOI: 10.1016/j.jaad.2009.09.016

[97] Shimizu K, Hashimoto T, Wang N, et al. A case of herpetiform pemphigus associated with autoimmune hemolytic anemia: Detection of autoantibodies against multiple epidermal antigens. Dermatology. 1996;**192**:179-182

[98] Sanchez-Palacios C, Chan LS. Development of pemphigus herpetiformis in a patient with psoriasis receiving UV-light treatment. Journal of Cutaneous Pathology. 2004;**31**:346-349

[99] Kubota Y, Yoshino Y, Mizoguchi M. A case of herpetiform pemphigus associated with lung cancer. The Journal of Dermatology. 1994;**21**:609-611

[100] Lu Y, Zhang M. Pemphigus herpetiformis in a patient with well-differentiated cutaneous angiosarcoma: Case report and review of the published work. The Journal of Dermatology. 2012;**39**:89-91. DOI: 10.1111/j.1346-8138.2011.01287.x

[101] Marzano AV, Tourlaki A, Cozzani E, Gianotti R, Caputo R. Pemphigus herpetiformis associated with prostate cancer. Journal of the European Academy of Dermatology and Venereology. 2007;**21**:696-698

[102] Yasuda H, Kobayashi H, Hashimoto T, et al. Subcorneal pustular dermatosis type of IgA pemphigus: Demonstration of autoantibodies to desmocollin-1 and clinical review. The British Journal of Dermatology. 2000;**143**:144-148

[103] Wallach D. Intraepidermal IgA pustulosis. Journal of the American Academy of Dermatology. 1992;**27**:993-1000. PMID: 1479108

[104] Szturz P, Adam Z, Klincová M, et al. Multiple myeloma associated IgA pemphigus: Treatment with bortezomib- and lenalidomide-based regimen. Clinical Lymphoma, Myeloma & Leukemia. 2011;**11**:517-520. DOI: 10.1016/j.clml.2011.06.014

Chapter 3

Bullous Pemphigoid

Derya Yayla, Pelin Hizli and Yeşim Yayla

Additional information is available at the end of the chapter

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Abstract

Bullous pemphigoid (BP) is a chronic, acquired, autoimmune bullous disease characterized by subepidermal bullae. It is usually seen in the elderly but, rarely, may also be seen in children. Autoantibodies against hemidesmosomal proteins BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen) are blamed for the pathogenesis. Clinically, it is characterized by large, tense blisters. Blisters can occur on normal skin or erythematous base with a predilection of flexural aspects of the limbs, abdomen, groin and axillae. Mucous membrane involvement is seen in about 10–35% of the patients. For treatment, general maintenance of BP patients is the first step. Systemic steroids are the common treatment agents. But localized disease can be treated successfully with topical corticosteroids. The common immunosuppressive agents are azathioprine, mycophenolate mofetil, methotrexate, chlorambucil and less often cyclophosphamide. In a minority of resistant cases, intravenous immunoglobulins, plasma exchange, anti-CD20 immunotherapy (rituximab), leflunomide, chlorambucil and methotrexate may be effective.

Keywords: blistering diseases, tense bullae, BP230, BP180, gestational pemphigoid

1. Introduction

Bullous pemphigoid (BP) is a chronic, acquired, autoimmune bullous disease characterized by subepidermal bullae [1–4]. It is the most common bullous disease, and its incidence has been gradually increasing [2, 5]. It is usually seen in the elderly, but rarely may also be seen in children [2, 6, 7]. In general, the clinical manifestations are tense bullae, urticarial lesions and intense pruritus [3, 5, 7]. Although mucosal findings are not common, oral findings are observed in 10–25% of cases [4, 5]. Autoantibodies against hemidesmosomal proteins BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen) are blamed for the pathogenesis [2].

2. History

In 1953, Walter Lever, M.D. was the first who described that BP was a distinct disease from pemphigus [8, 9]. In 1967, Jordon, Beutner et al. demonstrated the circulating autoantibodies against the epidermal basal membrane zone (BMZ) in patients with bullous pemphigoid using the immunofluorescence method [9].

3. Epidemiology

The annual incidence is approximately 6–7 new cases per million [8]. While the incidence in Europe ranges from 7 to 43 per million [10], this rate is 2.6 per million in Basra and 14 per million in the North East Scotland [2]. It is often seen in the elderly population (particularly in over 65 years of age) and more frequent in men [5, 11]; however, it has been cited in many studies that it is seen with equal frequency in both genders [4]. Patients older than 90 years have also a relative risk 300 times higher than those younger than 60 years [5]. Although it is rare in children, its incidence has been increasing [7]. In addition, there are no geographical or ethnic differences [4, 8].

4. Etiology

4.1. Genetic factors

No strong association was found with any of the HLA class I and II DR antigens [12]. Nevertheless, in some studies, HLA class II alleles were found to be more frequent in BP patients than in the general population [11]. A significant association with DQB1*0301 alleles was also found in Caucasians, while there was an association with DRB1*04, DRB1*1101 and DQB1*0302 alleles in Japanese patients [11]. In some studies, residual essential amino acids were detected in positions 71–77 of the DQB1 gene in patients with BP [5].

4.2. Environmental factors

It has been shown that furosemide, psoralen, ibuprofen, galantamine, hydrobromide, ACEi, spironolactone, penicillin, levofloxacin, metronidazole may lead to BP [13]. Adalimumab and etanercept (TNF-alpha blockers) associated BP cases have also been reported [5]. Another cause blamed in the etiology is vaccinations. BP may develop after 1 day–4 weeks of vaccination. In particular, most infantile BP cases have been described after the first dose [14]. In addition, trauma, radiotherapy and UVB exposure may cause bullous lesions by uncovering BP antigens [5]. In contrast to pemphigus vulgaris, no relationship between any dietary factor and BP has been found yet [5].

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5. Accompanying diseases

The incidence of malignancy is increased in BP cases (stomach cancer, lung cancer, etc.) [8, 15, 16]. There is also an increase in the incidence of psoriasis [8]. Although the immunogenetic and immunopathological mechanisms are not clear, it is considered that treatments for psoriasis (such as UVA-UVB) may play a trigger role for BP [8]. Another association is autoimmune diseases. BP is accompanied by some diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, dermatomyositis and autoimmune thrombocytopenia [8]. In addition, multiple sclerosis, dementia, stroke, epilepsy, Parkinson's disease, Shy-Drager syndrome and ALS are the most common neurological diseases in BP patients [10]. Although the mechanism is not clearly understood, BP1 and BP2 antigens are considered to play a role as autoreactive antigens in brain and skin [10].

6. Pathogenesis

BP is a subepidermal bullous disease with autoantibodies against hemidesmosomal proteins, BP 180 and 230 [17]. Hemidesmosomes are cellular adhesion proteins that bind basal keratinocytes to the extracellular matrix of the epidermis [5]. BP180 is a type 2 transmembrane protein kinase, also known as collagen XVII, while BP230 is a cytoplasmic protein [5]. The main target in BP is the noncollagenous region of BP180 (NC16A). Both IgG- and IgE-type autoantibodies against this structure are developed [3].

The role of BP230 is not clearly known in pathogenesis [18]. Many studies support that anti-BP230 antibodies play an important role in the onset of clinical symptoms and in the bulla formation [19]. Only anti-BP230 antibodies are detected in the serum of a few patients, while both anti-BP180 and anti-BP230 antibodies are present in all BP patients [18].

Anti-BP180 autoantibody titers were found to correlate with disease activity, itch intensity, peripheral blood eosinophil count and disease duration [17, 18, 20]. This correlation could not be obtained with anti-BP230 autoantibody titers [18].

In addition, a significant increase in total serum IgE levels was observed in 75–77% of patients with BP [3, 20]. IgE autoantibodies are against the NC16A region of BP180, as in IgG [3]. These autoantibodies were injected into mice, and urticarial lesions were detected [3, 21].

In patients with BP, an autoreactive T-cell response against BP180 and BP230 develops, which stimulates B cells to produce pathogenic autoantibodies [11]. These T lymphocytes are in the CD4+ phenotype and produce both Th1 (e.g., INF-gamma) and Th2 cytokines (such as IL-4, IL-5 and IL-13), and their major epitopes are located on NC16 domain [11]. Th2 cytokines are especially important in the pathogenesis of the disease and with their release, IgG4-type autoantibodies against BP180 are developed [11].

Unlike the pemphigus group of diseases, the autoantibodies deposited in the BMZ are not sufficient to cause disease emergence [22]. After antigen–antibody reaction, complement deposition

and activation of both classical and alternative pathways are necessary for subepidermal bulla development [23]. IgG and IgE autoantibodies against BP180 activate the complement system, which triggers the onset of inflammatory events [1, 5]. Therefore, mast cell degranulation and the release of TNF alpha, PAF and other cytokines, matrix metalloproteinase 9 and leukotrienes occur [1, 5, 11]. Proteolytic enzymes released from eosinophils and neutrophil elastase break-down various extracellular matrix proteins and BP180 [9, 11]. Proinflammatory mediators such as protease, IL-5 and eotaxin are released from infiltrating eosinophils, contributing to tissue damage [11]. In conclusion, BP180 autoantibodies directly stimulate keratinocytes to express various cytokines (such as IL-6, IL-8) and enhance inflammatory response [11].

A variant of BP, namely pemphigoid gestationis (PG) is one of the rare, pregnancy-specific bullous dermatoses, also known as herpes gestationis [24, 25]. Usually occurring in the second or third trimester of pregnancy, it is characterized by vesiculobullous rashes [24]. The disease can be seen in any trimester of the pregnancy as well as postpartum [26]. The incidence ranges from 1/50.000 to 1/1700 [24, 27]. The triggering factors are not known [27]. Graves' disease is the most commonly detected secondary autoimmune disease [24]. Rarely, it may also be associated with hydatidiform mole and chorionic epithelioma [24].

John Laws Milton first described the disease in 1872, as herpes gestationis [24]. Although the pathophysiology of PG has not been clearly explained, it is considered that MHCII antigens present in the placenta lead to an immunological response with a cross-reaction to the maternal skin [24]. HLA DR3 and HLA DR4 antigens were more frequently detected in these patients [25, 26].

The pathogenesis is similar to BP, and there are autoantibodies against the NC16A domain of BP2 antigen [25, 26]. In 10% of patients, autoantibodies against BP1 antigen are present [26]. Following this antigen-antibody interaction, complement activation takes place, and eosinophil chemotaxis occurs in the BMZ, where the antigen-antibody complex is present [25]. Eosinophil degranulation also leads to damage in the dermoepidermal region and bulla formation [25].

7. Clinical features

BP shows a clinical polymorphism [28]. Clinically, it is characterized by large, tense blisters. Blisters can occur on normal skin or erythematous base with a predilection of flexural aspects of the limbs, abdomen, groin and axillae [29]. The most common initial clinical presentations are pruritic eczema or urticarial-like erythema without blisters and it is called nonbullous phase [30, 31]. Itching of various degrees may be seen in the course of the disease. However, significant pruritus is more frequent, and therefore, it may be the only manifestation of the disease, especially in older patients [30, 32].

BP commonly starts with pruritus and nonspecific skin lesions. Pruritus may persist for many months before the eruption [30, 33]. Therefore, physicians should consider BP in differential

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diagnosis of elderly patients with long-term persisting pruritus and nonspecific eczema-like or urticarial lesions [31]. Blisters frequently occur after 1–3 weeks of nonbullous phase. Nonbullous urticarial lesions may stay several months before the blisters occur [33].

In bullous stage, vesicles and bullae appear on normal or erythematous skin together with urticarial and infiltrated papules with an annular or figurate pattern [34]. Blisters are tense, filled with serous fluid, sometimes hemorrhagic, and Nikolsky sign is negative (**Figure 1**) [29, 34, 35].

Blisters usually appear in symmetric distribution. A central resolution commonly occurs, and postinflammatory hyperpigmentation and milia may be seen. Additionally, persistent erythema may occur and remain for many weeks at the site of the prior blisters [29, 33, 36].

Mucous membrane involvement is seen in about 10–35% of the patients. Most affected mucous membrane is buccal mucosa [29]. In buccal mucosa, mucosal erosions are common, while intact blisters are rare [37]. Involvement of other mucosal sites like nose, esophagus, pharynx or anogenital system is relatively rare [34].

Unusual clinical variants of BP previously described depending on different clinical presentations are as follows: dyshidrosiform BP, intertrigo-like BP, prurigo-nodularis-like BP, vesicular BP, papular BP, eczematous BP, erythrodermic BP, lymphomatoid papulosis-like BP, lichen planus pemphigoides and BP with TEN-like lesions.

Several different localized forms are pretibial BP, peristomal BP, umbilical BP, vulvar BP, stump pemphigoid (distal end of amputated limbs), BP on paralyzed limbs, BP on body sites of radiotherapy [34, 35, 38]. The most common localized form is pretibial BP. Another localized form is vulvar BP and is seen in young girls presenting with vulvar erosions, blisters and ulcers. Localized forms either may not progress for years or generalization may occur [29, 37].

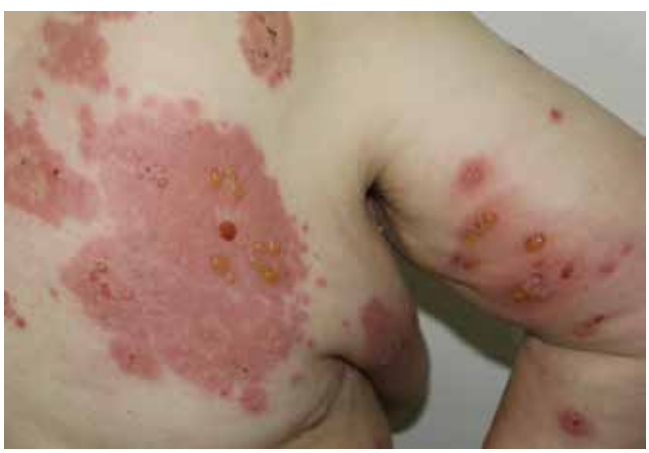

Figure 1. Nikolsky negative blisters and erythematous plaques on upper extremity and shoulders.

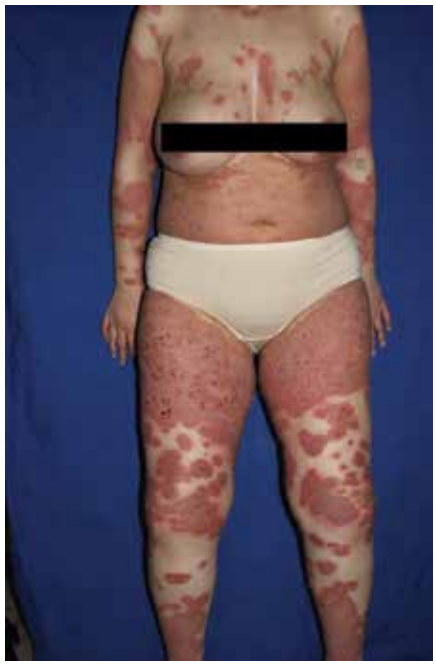

Figure 2. Targetoid lesions and erythematous eruptions involving upper and lower extremities.

Pemphigoid nodularis is a rare clinical type of BP commonly seen in elderly women. It may present with prurigo-nodularis-like intensely itchy nodules, papules and BP-like blisters together [39, 40].

In childhood BP, there are some clinical differences. Commonly, the disease first appears acrally in infants and then may generalize. The face, palms and soles are frequently affected. Genital involvement is seen in older children [41]. In most children, the disease lasts less than 1 year [37].

PG is a special clinical variant of BP seen especially during late pregnancy, but it may occur at any time of pregnancy or immediately after delivery. In general, it starts from the abdomen, especially from periumbilical region as urticarial erythema. Then, herpetiform vesicles may occur at the periphery of the erythema. Tense bullae on erythematous base may also be present [35, 42]. Rapidly, it may progress to a pemphigoid-like eruption involving entire body (**Figure 2**). Generally, face, scalp and oral mucosa are not affected.

After delivery, flare of the disease is seen in 75% of patients, and in some patients, explosive onset of blistering occurs within hours. Usually, PG disappears spontaneously within 3 months after delivery [34, 37]. Recurrences may be associated with menstruation and oral contraceptive usage. In subsequent pregnancies, recurrence with early onset and a more severe disease are common [37].

Ten percent of newborns develop skin lesions due to the maternal antibodies [34]. But the eruption is self-limited and does not need treatment [29].

8. Histology

The most valuable diagnostic biopsy for BP is that taken from early small blisters [29]. The histopathologic findings of BP under light microscopy are subepidermal bullae without acantholysis and eosinophil-rich superficial dermal infiltrate.

The amount of superficial dermal infiltrate varies, as does the cellular content. Hence, the biopsies may be categorized as granulocyte-rich and granulocyte-poor, depending on whether the biopsy was taken form inflamed or noninflamed region. Eosinophils are usually the predominant inflammatory cells of the infiltrate, whereas some biopsies may show neutrophil predominance [37, 43].

In urticarial lesions at the prodromal stage, the histopathologic findings may not be specific. There may be only a superficial dermal infiltrate of lymphocytes, histiocytes and abundant eosinophils with papillary dermal edema and eosinophilic spongiosis occasionally [44].

9. Special tests

In 23% of BP patients, biopsies were not used in the diagnosis of BP; at that point, direct immunofluorescence (DIF), indirect immunofluorescence (IIF) and ELISA are critical for correct diagnosis [37].

In almost all patients, direct IF of perilesional healthy skin shows thin, linear (tubular or toothpaste pattern) and continuous deposition of IgG and/or C3 along the BMZ [45–49]. Predominantly, the deposition of IgG1 and IgG4 has been shown; also, all IgG subclasses and IgE have been reported. False-negative results are more common on lower extremities. Close analysis of the pattern of immune deposition may be helpful for us to differentiate autoimmune blistering diseases. For example, there is an n-serrated pattern in BP and linear IgA bullous dermatosis and u-serrated pattern in epidermolysis bullosa acquisita EBA [50].

There are circulating anti-basement membrane zone IgG and IgE autoantibodies in 60–80% (approximately 70%) of the BP patients [47–49, 51–56]. These autoantibodies typically bind to epidermal side of 1 M NaCl-split human skin substrate or less often binds to both dermal and epidermal sides. Even if not routinely used, computer-aided fluorescence overlay antigen mapping (FOAM) shows the exact localization of the immune deposition [56]. For IIF, 1 M NaCl-split human skin is rather preferred than intact human skin or monkey esophagus. By incubating the human skin with 1 M NaCl, the epidermis will be separated from the dermis at lamina lucida. Using 1 M NaCl-split skin substrate has another advantage, and it can be used

to differentiate BP from EBA. EBA autoantibodies bind to the base or the floor of the split skin (i.e., dermal side), but BP autoantibodies bind to the roof of it (i.e., epidermal side).

This is not the only histological difference between EBA and BP. C3 deposition is sometimes absent in EBA but is nearly always present in BP, and type-4 collagen stains the roof of the blister in EBA, whereas it stains the base in BP. In more than 70% of patients, there are circulating anti-BMZ autoantibodies [57, 58]. Unlike pemphigus, in BP, circulating IIF autoantibody levels do not show the disease activity or the extent of the disease [59].

ELISA has been found to be fairly specific (90%), especially ELISA that is using recombinant proteins, which bind to specific regions of the BP antigens like the NC16A part of BP180 and the C-terminus of BP180 or BP230 [60, 61]. ELISA has also proven to be sensitive for detecting the circulating antigen-specific IgG and IgE autoantibodies, so for that reason, ELISA is useful in both research and clinical settings. ELISA tests are commercially available with sensitivity of 89% and specificity of 98% [62].

Almost three out of four patients have antigen-specific IgE detectable by IF and ELISA [20, 54, 63–67]. Patients with antigen-specific IgE antibody may develop more severe form of disease. IgE plays a role in attracting eosinophils to skin lesions, so patients with antigen-specific IgE antibody may develop instant urticarial-like lesions [21, 65, 66].

Sometimes, elderly patients with pruritic cutaneous eruptions or healthy subjects have low titer false-positive results. Approximately 7% of the normal population has anti-BP180 antibodies detectable by ELISA but shows no clinical or histological features of the disease; therefore, ELISA must be used in appropriate conditions not as a screening method [68].

Similar to BP, the main diagnostic marker of PG is the linear deposition of C3 along BMZ of perilesional healthy skin. The linear deposition of C3 is observed in 100%, but linear IgG deposition is only seen in 30% of PG patients. On conventional IIF testing, nearly 30% of PG patients have a circulating IgG anti-basement zone antibody. But when complement-enhanced IIF testing is used, nearly 75% of patients show PG factor (a complement-fixing anti-BMZ IgG1 autoantibody) [34].

10. Treatment

General maintenance of the patient is the first step in the treatment of BP patients. It is important to drain the large blisters because the serous fluid inside the blisters makes an essential environment for infections. If there is any local pain, infection possibility should be kept in mind and after taking wound culture, a proper antibiotic has to be started.

Treatment of BP depends on the extent of disease and mostly on clinical experience rather than controlled clinical trials [69–79].

Systemic steroids are the common treatment agents. But localized disease can be treated successfully with topical corticosteroids [48, 49, 80]. In recent studies, clobetasol propionate

cream 0.5% was applied twice daily to the entire surface of the body so the patients received a daily dose of 40 g [72]. This amount of high-potency topical corticosteroid may result in high systemic absorption and can cause local and systemic side effects [81]. This kind of topical treatment is very difficult and expensive to apply, and these controlled studies did not emphasize the patients' ability to reach complete disease-free period as with systemic corticosteroids. Nevertheless, potent topical corticosteroids can control even generalized BP and may be safer than oral corticosteroids [77–79, 81]. Topical tacrolimus can also be a useful agent in some cases of localized pemphigoid [80, 82–85].

Patients with generalized disease are usually treated with oral prednisone [80, 86, 87]. For more extensive disease, a regimen of oral prednisone at a dose of 0.5–1 mg/kg/day can control the disease within 1–2 weeks. Afterwards, the dose can be tapered over a period of 6–9 months. On some occasions, pulse methyl prednisolone therapy may be required for rapid controlling of active blister formation [88]. Systemic corticosteroids are always associated with serious side effects (like osteoporosis, diabetes and immunosuppression) and in elderly patients, these side effects may be even more severe [89].

In order to minimize the side effects of oral glucocorticosteroids, immunosuppressive drugs can be used in conjunction with prednisone [80, 87, 90–96]. However, there are very few controlled trials for this common approach. The use of immunosuppressive drugs is controversial. They can also be used as second-line therapy if corticosteroids are contraindicated or fail to control the disease. The common immunosuppressive agents are azathioprine, mycophenolate mofetil (1.5–3 g/day), methotrexate, chlorambucil (0.1 mg/kg/day, frequently 4–6 mg/day), and less often cyclophosphamide (1–3 mg/kg/day). The dosage of azathioprine (0.5–2.5 mg/kg/day) is adjusted by thiopurine methyltransferase level, with this adjustment, the efficacy of azathioprine will increase and side effects will be decreased. Choosing an immunosuppressive agent primarily depends on side effect profile, patients' general status and doctors' experience.

When corticosteroids are contraindicated, few reports have described successful treatment of some patients with the combination of nicotinamide (500–2000 mg/day) and minocycline or tetracycline or erythromycin; or tetracycline alone [97, 98]. Sulfones can be used to treat some patients. If there is no glucose-6-phosphate dehydrogenase deficiency, dapsone and sulfapyridine have been reported to control the disease activity in 15–44% of BP patients [87, 99–101]. In a minority of resistant cases, intravenous immunoglobulins (IVIg) [102–104], plasma exchange [73], anti-CD20 immunotherapy (rituximab) [105–107], leflunomide [108], chlorambucil [109] and methotrexate [92, 94, 110] may be effective.

Even if the duration of treatment has not been clear yet, BP patients generally need to be treated for about 12–18 months. This period of time includes both active disease treatment and also a maintenance phase after cessation of active disease. This maintenance phase lasts for about 3–6 months, and during this phase, low-dose oral prednisone (<10 mg/day) or topical clobetasol propionate (10 g/week) is used [111]. As previously mentioned, initial doses of prednisone of 0.5–1.0 mg/kg/day or even less can control the disease. After new blister formation has stopped and erythema has disappeared—this usually has happened within 1–2 weeks—progressive tapering of prednisone over a 6–9-month period or rarely longer is recommended. Lowering the dose of 5 mg for every week until reaching 30 mg is commonly used. The patients' clinical

response should be monitored carefully, and lowering of the prednisone dose should be done according to this response. Because of the side effects of glucocorticoids, it is important to minimize the total dose and duration of the treatment. It is important to eliminate the complications of glucocorticoids by using osteoporosis prophylaxis and gastric protection, monitoring the cardiovascular function and infection risk [35].

BULLOUS PEMPHIGOID TREATMENT STEPS
General maintenance
Drainage of blisters
Prevention of local infections
Localized disease
Super potent topical corticosteroids (e.g., clobetasol propionate)
Topical immunomodulators (e.g., tacrolimus)
Nicotinamide in association with minocycline, doxycycline or tetracycline
Erythromycin
Dapsone, sulfonamides
Extensive or refractory disease
Oral corticosteroids
Azathioprine
Mycophenolate mofetil
Methotrexate
Chlorambucil
Cyclophosphamide
IVIg
Plasma exchange
Rituximab

The treatment of PG is similar to that of BP. But teratogenic side effects of some therapeutical agents for BP limit their usage during pregnancy. Mild cases of PG can be successfully treated with topical corticosteroids. But halogenated corticosteroids can cross the placenta, so class 6 and 7 corticosteroids are the safest (e.g., mometasone furoate, prednicarbate, methylprednisolone aceponate). For systemic treatment, prednisolone is the main choice because it is largely inactivated in the placenta (mother:fetus = 10:1). During the first trimester, especially between 8 and 11 weeks, there is a slightly increased risk of cleft lip/cleft palate. Nevertheless, if dosages are <10–15 mg/day, it appears to be safe. But for long-term use, risk of adrenal insufficiency in the newborn should be kept in mind, and fetal growth should also be monitored [112]. A few refractory cases may be treated with dapsone, doxycycline or minocycline ± nicotinamide, pyridoxine, cyclosporine, methotrexate, cyclophosphamide, gold and IVIg. But all these agents

with the exception of cyclosporine and IVIg should be avoided during pregnancy period. Plasmapheresis may be a rather safe treatment option during pregnancy if corticosteroid is contraindicated or fails to control the disease [34].

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References

[1] Qiao P, Dang E, Cao T, Fang H, Zhang J, Qiao H, Wang G. Dysregulation of mCD46 and sCD46 contribute to the pathogenesis of bullous pemphigoid. Scientific Reports. 2017; **7**(1):145. DOI: 10.1038/s41598-017-00235-3

[2] Leuci S, Gürcan HM, Ahmed AR. Serological studies in bullous pemphigoid: A literature review of antibody titers at presentation and in clinical remission. Acta Dermato-Venereologica. 2010;**90**(2):115-121. DOI: 10.2340/00015555-0819

[3] Kalowska M, Ciepiela O, Kowalewski C, Demkow U, Schwartz RA, Wozniak K. Enzyme-linked immunoassay index for anti-NC16a IgG and IgE auto-antibodies correlates with severity and activity of bullous pemphigoid. Acta Dermato-Venereologica. 2016;**96**(2):191-196. DOI: 10.2340/00015555-2101

[4] Patrício P, Ferreira C, Gomes MM, Filipe P. Autoimmune Bullous dermatoses: A review. Annals of the New York Academy of Sciences. 2009;**1173**:203-210. DOI: 10.1111/j.1749-6632.2009.04737

[5] Patel F, Wilken R, Patel FB, Sultani H, Bustos I, Duong C, Zone JJ, Raychaudhuri SP, Maverakis E. Pathophysiology of autoimmune bullous diseases: Nature versus nurture. Indian Journal of Dermatology. 2017;**62**(3):262-267. DOI: 10.4103/0019-5154.159620

[6] Osawa M, Ueda-Hayakawa I, Isei T, Yoshimura K, Fukuda S, Hashimoto T, Okamoto H. A case of childhood bullous pemphigoid with IgG and IgA autoantibodies to various domains of BP180. Journal of the American Academy of Dermatology. 2014;**70**(6):e129-e131. DOI: 10.1016/j.jaad.2013.06.006

[7] Schwieger-Briel A, Moellmann C, Mattulat B, Schauer F, Kiritsi D, Schmidt E, Sitaru C, Ott H, Kern JS. Bullous pemphigoid in infants: Characteristics, diagnosis and treatment. Orphanet Journal of Rare Diseases. 2014;**10**(9):185. DOI: 10.1186/s13023-014-0185-6

[8] Stoica LE, Patrascu V, Dascalu RC, Ciurea ME. Bullous pemphigoid associated with psoriasis, breast cancer and Parkinson's disease. Current Health Science Journal. 2014; **40**(1):62-66. DOI: 10.12865/CHSJ.40.01.12

[9] Kasperkiewicz M, Zillikens D. The pathophysiology of bullous pemphigoid. Clinical Reviews in Allergy and Immunology. 2007;**33**(1–2):67-77

[10] Tarazona MJ, Mota AN, Gripp AC, Unterstell N, Bressan AL. Bullous pemphigoid and neurological disease: Statistics from a dermatology service. Anais Brasileiros de Dermatologia. 2015;**90**(2):280-282. DOI: 10.1590/abd1806-4841.20153334

[11] Bolognia JL, Jorizzo JL, Rapini RP. Dermatoloji. Elsevier Limited. 2012:431-438

[12] Taylor G, Venning V, Wojnarowska F, Welch K. Bullous pemphigoid and autoimmunity. Journal of the American Academy of Dermatology. 1993;**29**(2 Pt 1):181-184

[13] Moitra S, Sen S, Banerjee I, Sikder A, Das P. Metronidazole-induced bullous pemphigoid: A case report. Journal of Clinical and Diagnostic Research. 2015;**9**(12):FD01-FD03. DOI: 10.7860/JCDR/2015/14669.6972

[14] Bisherwal K, Pandhi D, Singal A, Sharma S. Infantile bullous Pemphigoid following vaccination. Indian Pediatrics. 2016;**53**(5):425-426

[15] Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. The Journal of Investigative Dermatology. 2015; **135**(5):1445-1447. DOI: 10.1038/jid.2014.547

[16] Ogawa H, Sakuma M, Morioka S, Kitamura K, Sasai Y, Imamura S, Inaba Y. The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. Journal of Dermatological Science. 1995;**9**(2):136-141

[17] Cai SC, Lim YL, Li W, Allen JC, Chua SH, Tan SH, Tang MB. Anti-BP180 NC16A IgG Titres as an indicator of disease activity and outcome in Asian patients with bullous pemphigoid. Annals of the Academy of Medicine, Singapore. 2015;**44**(4):119-126

[18] Patsatsi A, Kyriakou A, Pavlitou-Tsiontsi A, Giannakou A, Sotiriadis D. Association of autoantibodies to BP180 with disease activity in Greek patients with bullous pemphigoid. Clinical & Developmental Immunology. 2012;**854795**. DOI: 10.1155/2012/854795

[19] Mueller S, Klaus-Kovtun V, Stanley JR. A 230-kD basic protein is the major bullous pemphigoid antigen. The Journal of Investigative Dermatology. 1989;**92**(1):33-38

[20] Messingham KA, Noe MH, Chapman MA, Giudice GJ, Fairley JA. A novel ELISA reveals high frequencies of BP180-specific IgE production in bullous pemphigoid. Journal of Immunology Methods. 2009 July 31;**346**(1–2):18-25. DOI: 10.1016/j.jim.2009.04.013

[21] Fairley JA, Burnett CT, Fu CL, Larson DL, Fleming MG, Giudice GJ. A pathogenic role for IgE in autoimmunity: Bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to nu/nu mice. The Journal of Investigative Dermatology. 2007;**127**(11):2605-2611

[22] Liu Z, Giudice GJ, Zhou X, Swartz SJ, Troy JL, Fairley JA, Till GO, Diaz LA. A major role for neutrophils in experimental bullous pemphigoid. The Journal of Clinical Investigation. 1997;**100**(5):1256-1263

[23] Nelson KC, Zhao M, Schroeder PR, Li N, Wetsel RA, Diaz LA, Liu Z. Role of different pathways of the complement cascade in experimental bullous pemphigoid. The Journal of Clinical Investigation. 2006;**116**(11):2892-2900

[24] Stevenson ML, Marmon S, Tsou H, Boyd KP, Robinson MR, Meehan SA, Pomerantz R. Pemphigoid gestationis. Dermatology Online Journal. 2013;**19**(12):20715

[25] Cobo MF, Santi CG, Maruta CW, Aoki V. Pemphigoid gestationis: Clinical and laboratory evaluation. Clinics (São Paulo, Brazil). 2009;**64**(11):1043-1047. DOI: 10.1590/S1807-59322009001100002

[26] Huilaja L, Mäkikallio K, Tasanen K. Gestational pemphigoid. Orphanet Journal of Rare Diseases. 2014;**9**:136. DOI: 10.1186/s13023-014-0136-2

[27] Singla A, Shree S, Mehta S. Pregnancy with pemphigoid gestationis: A rare entity. Journal of Clinical and Diagnostic Research. 2016;**10**(7):QD06-QD07. DOI: 10.7860/JCDR/2016/19491.8215

[28] Di Zenzo G, Della Torre R, Zambruno G, Borradori L. Bullous pemphigoid: From the clinic to the bench. Clinics in Dermatology. 2012;**30**(1):3-16

[29] Stanley J: Bullous pemphigoid. In: Fitzpatrick's dermatology in general medicine. Volume 1, 7th edition. Edited by Fitzpatrick TB, Wolff K. New York: McGraw-Hill Medical; 2008:475-480

[30] Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. Autoimmunity Reviews. 2014;**13**(4–5):482-489

[31] Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 1: Clinical manifestations. Journal der Deutschen Dermatologischen Gesellschaft. 2011;**9**(10):844-856; quiz 857

[32] Bakker CV, Terra JB, Pas HH, Jonkman MF. Bullous pemphigoid as pruritus in the elderly: A common presentation. JAMA Dermatology. 2013;**149**(8):950-953

[33] Wojnarowska F, Venning V. Immunobullous diseases. In: Burns TF, Rook A, editors. Rook's Textbook of Dermatology. 8th ed. Oxford: Wiley-Blackwell; 2010. pp. 1895-1956

[34] Borradori L BP: Vesiculobullous diseases. In: Jean L. Bolognia, Joseph L. Jorizzo, Ronald P. Rapini; associate and artwork editor, Julie V. Schaffer. Dermatology (Basel, Switzerland). Volume 1, 2nd ed.St. Louis, Mo.; London: Mosby Elsevier; 2008:431-445

[35] Schmidt E, della Torre R, Borradori L. Clinical features and practical diagnosis of bullous pemphigoid. Immunology and Allergy Clinics of North America. 2012;**32**(2):217-232

[36] Amber KT, Murrell DF, Schmidt E, Joly P, Borradori L. Autoimmune subepidermal bullous diseases of the skin and mucosae: Clinical features, diagnosis, and management. Clinical Reviews in Allergy and Immunology. 2017

[37] James WD, Elston DM, Berger TG. Andrews' Diseases of the Skin: Clinical Dermatology, 10th Edn. London: Saunders Elsevier; 2006

[38] Liu HN, Su WP, Rogers RS 3rd. Clinical variants of pemphigoid. International Journal of Dermatology. 1986;**25**(1):17-27

[39] Kwong HL, Lim SP. Pemphigoid nodularis mimicking nodular prurigo in an immune-suppressed patient with rheumatoid arthritis. Acta dermato-venereologica. 2015;**95**(2): 237-238

[40] Powell AM, Albert S, Gratian MJ, Bittencourt R, Bhogal BS, Black MM. Pemphigoid nodularis (non-bullous): A clinicopathological study of five cases. The British Journal of Dermatology. 2002;**147**(2):343-349

[41] Waisbourd-Zinman O, Ben-Amitai D, Cohen AD, Feinmesser M, Mimouni D, Adir-Shani A, Zlotkin M, Zvulunov A. Bullous pemphigoid in infancy: Clinical and epidemiologic characteristics. Journal of the American Academy of Dermatology. 2008;**58**(1):41-48

[42] Lipozencic J, Ljubojevic S, Bukvic-Mokos Z. Pemphigoid gestationis. Clinics in Dermatology. 2012;**30**(1):51-55

[43] Yancey KB. The pathophysiology of autoimmune blistering diseases. The Journal of Clinical Investigation. 2005;**115**(4):825-828

[44] Murrell D. Blistering Diseases: Clinical Features, Pathogenesis, Treatment. Berlin: Springer; 2015

[45] Beutner EH et al. Autoantibodies in pemphigus vulgaris: Response to an intercellular substance of epidermis. Journal of the American Medical Association. 1965;**192**:682

[46] Jordon RE et al. Basement zone antibodies in bullous pemphigoid. Journal of the American Medical Association. 1967;**200**(9):751

[47] Person JR, Rogers RS 3rd. Bullous and cicatricial pemphigoid. Clinical, histopathologic, and immunopathologic correlations. Mayo Clinic Proceedings. 1977;**52**(1):54

[48] Hadi SM et al. Clinical, histological and immunological studies in 50 patients with bullous pemphigoid. Dermatologica. 1988;**176**(1):6

[49] Ahmed AR, Maize JC, Provost TT. Bullous pemphigoid. Clinical and immunologic follow-up after successful therapy. Archives of Dermatology. 1977;**113**(8):1043

[50] Vodegel RM, Jonkman MF, Pas HH, de Jong MC. U-serrated immunodeposition pattern differentiates type VII collagen targeting bullous diseases from other subepidermal bullous autoimmune diseases. The British Journal of Dermatology. 2004;**151**:112-118

[51] Dimson OG et al. Identifiation of a potential effector function for IgE autoantibodies in the organ-specifi autoimmune disease bullous pemphigoid. The Journal of Investigative Dermatology. 2003;**120**(5):784

[52] Bushkell LL, Jordon RE. Bullous pemphigoid: A cause of peripheral blood eosinophilia. Journal of the American Academy of Dermatology. 1983;**8**(5):648

[53] Beutner EH, Jordon RE, Chorzelski TP. The immunopathology of pemphigus and bullous pemphigoid. The Journal of Investigative Dermatology. 1968;**51**(2):63

[54] Fairley JA, Fu CL, Giudice GJ. Mapping the binding sites of anti-BP180 immunoglobulin E autoantibodies in bullous pemphigoid. The Journal of Investigative Dermatology. 2005;**125**(3):467

[55] Parodi A, Rebora A. Serum IgE antibodies bind to the epidermal side of the basement membrane zone splits in bullous pemphigoid. The British Journal of Dermatology. 1992; **126**(5):526

[56] De Jong MC, Bruins S, Heeres K, et al. Bullous pemphigoid and epidermolysis bullosa acquisita. Differentiation by fluorescence overlay antigen mapping. Archives of Dermatology. 1996;**132**:151-157

[57] Gammon WR et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunoflorescence on 1.0 M sodium chloride-separated skin. The Journal of Investigative Dermatology. 1984;**82**(2):139

[58] Kelly SE, Wojnarowska F. The use of chemically split tissue in the detection of circulating antibasement membrane zone antibodies in bullous pemphigoid and cicatricial pemphigoid. The British Journal of Dermatology. 1988;**118**(1):31

[59] Sams WM Jr, Jordon RE. Correlation of pemphigoid and pemphigus antibody titres with activity of disease. The British Journal of Dermatology. 1971;**84**(1):7

[60] Zillikens D, Rose PA, Balding SD, et al. Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. The Journal of Investigative Dermatology. 1997;**109**:573-579

[61] Di Zenzo G, Marazza G, Borradori L. Bullous pemphigoid: Physiopathology, clinical features and management. Advances in Dermatology. 2007;**23**:257-288

[62] Sakuma-Oyama Y et al. Evaluation of a BP180-NC16a enzyme-linked immunosorbent assay in the initial diagnosis of bullous pemphigoid. The British Journal of Dermatology. 2004;**151**(1):126

[63] Christophoridis S et al. IgG, IgA and IgE autoantibodies against the ectodomain of BP180 in patients with bullous and cicatricial pemphigoid and linear IgA bullous dermatosis. The British Journal of Dermatology. 2000;**143**(2):349

[64] Dopp R et al. IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in bullous pemphigoid: Serum levels of these immunoglobulins reflect disease activity. Journal of the American Academy of Dermatology. 2000;**42**(4):577

[65] Ishiura N et al. Serum levels of IgE anti-BP180 and anti-BP230 autoantibodies in patients with bullous pemphigoid. Journal of Dermatological Science. 2008;**49**(2):153

[66] Iwata Y et al. Correlation of IgE autoantibody to BP180 with a severe form of bullous pemphigoid. Archives of Dermatology. 2008;**144**(1):41

[67] Woodley DT. The role of IgE anti-basement membrane zone autoantibodies in bullous pemphigoid. Archives of Dermatology. 2007;**143**(2):249

[68] Wieland CN et al. Anti-bullous pemphigoid 180 and 230 antibodies in a sample of [1] unaffected subjects. Archives of Dermatology. 2010;**146**(1):21

[69] Korman NJ. Bullous pemphigoid. Journal of the American Academy of Dermatology. 1987;**16**:907-924

[70] Joly P, Benichou J, Lok C, et al.: Prediction of survival for patients with bullous pemphigoid: A prospective study. Archives of Dermatology 2005;**141**:691-698

[71] Korman NJ. New and emerging therapies in the treatment of blistering diseases. Dermatologic Clinics. 2000;**18**:127-137

[72] Joly P et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. The New England Journal of Medicine. 2002;**346**:321-327

[73] Roujeau JC et al. Plasma exchange in bullous pemphigoid. Lancet. 1984;**2**:486-488

[74] Morel P, Guillaume JC. Treatment of bullous pemphigoid with prednisolone only: 0.75mg/kg/day versus 1.25mg/kg/day. A multicenter randomized study. Annales de Dermatologie et de Vénéréologie. 1984;**111**:925-928

[75] Guillot B, Donadio D, Guilhou JJ, et al. Long term plasma exchange therapy in bullous pemphigoid. Acta Dermato-Venereologica. 1986;**66**:73-75

[76] Dreno B, Sassolas B, Lacour P, et al. Methylprednisolone versus prednisolone methylsulfobenzoate in pemphigoid: A comparative multicenter study. Annales de Dermatologie et de Vénéréologie. 1993;**120**:518-521

[77] Guillaume JC, Vaillant L, Bernard P, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. Archives of Dermatology. 1993;**129**:49-53

[78] Fivenson DP, Breneman DL, Rosen GB, et al. Nicotinamide and tetracycline therapy of bullous pemphigoid. Archives of Dermatology. 1994;**130**:753-758

[79] Chan LS et al. Immune-mediated subepithelial blistering diseases of mucous membranes. Pure ocular cicatricial pemphigoid is a unique clinical and immunopathological entity distinct from bullous pemphigoid and other subsets identified by antigenic specificity of autoantibodies. Archives of Dermatology. 1993;**129**:448-455

[80] Fine JD. Management of acquired bullous skin diseases. The New England Journal of Medicine. 1995;**333**(22):1475

[81] Bystryn JC, Wainwright BD, Shupack JL. Oral and topical corticosteroids in bullous pemphigoid. The New England Journal of Medicine. 2002;**347**(2):143

[82] Chu J, Bradley M, Marinkovich MP. Topical tacrolimus is a useful adjunctive therapy for bullous pemphigoid. Archives of Dermatology. 2003;**139**(6):813

[83] Chuh AA. The application of topical tacrolimus in vesicular pemphigoid. The British Journal of Dermatology. 2004;**150**(3):622

[84] Ko MJ, Chu CY. Topical tacrolimus therapy for localized bullous pemphigoid. The British Journal of Dermatology. 2003;**149**(5):1079

[85] Lebeau S et al. Localized childhood vulval pemphigoid treated with tacrolimus ointment. Dermatology. 2004;**208**(3):273

[86] Patton T, Korman NJ. Bullous pemphigoid treatment review. Expert Opinion on Pharmacotherapy. 2006;**7**(17):2403

[87] Wojnarowska F et al. Guidelines for the management of bullous pemphigoid. The British Journal of Dermatology. 2002;**147**(2):214

[88] Siegel J, Eaglstein WH. High-dose methylprednisolone in the treatment of bullous pemphigoid. Archives of Dermatology. 1984;**120**(9):1157

[89] Savin JA. The events leading to the death of patients with pemphigus and pemphigoid. The British Journal of Dermatology. 1979;**101**(5):521

[90] Bohm M et al. Bullous pemphigoid treated with mycophenolate mofetil. Lancet. 1997; **349**(9051):541

[91] Burton JL et al. Azathioprine plus prednisone in treatment of pemphigoid. British Medical Journal. 1978;**2**(6146):1190

[92] Gurcan HM, Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. The British Journal of Dermatology. 2009; **161**(4):723

[93] Heilborn JD et al. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. Journal of the American Academy of Dermatology. 1999;**40**(5 Pt 1):741

[94] Kjellman P, Eriksson H, Berg P. A retrospective analysis of patients with bullous pemphigoid treated with methotrexate. Archives of Dermatology. 2008;**144**(5):612

[95] Nousari HC, Griff WA, Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. Journal of the American Academy of Dermatology. 1998;**39**(3):497

[96] Paul MA, Jorizzo JL, Fleischer AB Jr, White WL. Low-dose methotrexate treatment in elderly patients with bullous pemphigoid. Journal of the American Academy of Dermatology. 1994;**31**(4):620

[97] Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide. A preliminary report. Archives of Dermatology. 1986;**122**(6):670

[98] Kolbach DN et al. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. The British Journal of Dermatology. 1995;**133**(1):88

[99] Bouscarat F et al. Treatment of bullous pemphigoid with dapsone: Retrospective study of thirtysix cases. Journal of the American Academy of Dermatology. 1996;**34**(4):683

[100] Person JR, Rogers RS 3rd. Bullous pemphigoid responding to sulfapyridine and the sulfones. Archives of Dermatology. 1977;**113**(5):610

[101] Venning VA, Millard PR, Wojnarowska F. Dapsone as fist line therapy for bullous pemphigoid. The British Journal of Dermatology. 1989;**120**(1):83

[102] Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. Journal of the American Academy of Dermatology. 2001;**45**(6):825

[103] Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Archives of Dermatology. 2003;**139**(8):1051

[104] Engineer L, Ahmed AR. Role of intravenous immunoglobulin in the treatment of bullous pemphigoid: Analysis of current data. Journal of the American Academy of Dermatology. 2001;**44**(1):83

[105] Silva N et al. Bullous pemphigoid successfully treated with rituximab. Acta Médica Portuguesa. 2017;**30**(3):243

[106] Nguyen T, Ahmed AR. Positive clinical outcome in a patient with recalcitrant bullous pemphigoid treated with rituximab and intravenous immunoglobulin. Clinical and Experimental Dermatology. 2017;**42**(5):516

[107] Bilgiç Temel A et al. Successful treatment of a bullous pemphigoid patient with rituximab who was refractory to corticosteroid and omalizumab treatments. Case Rep Dermatol. 2017;**9**(1):38

[108] Nousari HC, Anhalt GJ. Bullous pemphigoid treated with leflunomide: A novel immunomodulatory agent. Archives of Dermatology. 2000;**136**(10):1204

[109] Milligan A, Hutchinson PE. The use of chlorambucil in the treatment of bullous [110] pemphigoid. Journal of the American Academy of Dermatology. 1990;**22**(5 Pt 1):796

[110] Bara C et al. Methotrexate for bullous pemphigoid: Preliminary study. Archives of Dermatology. 2003;**139**(11):1506

[111] Bernard P, Reguiai Z, Tancrède-Bohin E, et al. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: A multicenter, prospective, cohort study. Archives of Dermatology. 2009;**145**:537-542

[112] Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2008

Chapter 4

Acquired Epidermolysis Bullosa and Linear Immunoglobulin A Bullous Dermatosis

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Additional information is available at the end of the chapter

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Abstract

Acquired epidermolysis bullosa is a rare subepidermal bullous disease characterized by autoantibodies to type VII collagen, the major component of anchoring fibrils. Although the exact pathophysiologic mechanism remains unclear, reduction or perturbation of the anchoring fibrils results subepidermal blister formation and clinical features such as skin fragility, blisters, erosions, scars, milia and nail loss. Acquired epidermolysis bullosa includes various clinical manifestations resembling genetic epidermolysis bullosa, bullous pemphigoid, cicatricial pemphigoid, Brunsting-Perry pemphigoid and linear immunoglobulin A bullous dermatosis. Numerous treatment options are available but patients are often refractory to treatment. Linear immunoglobulin A bullous dermatosis is another subepidermal bullous disease characterized by the accumulation of IgA antibodies in lamina densa or sublamina densa region of the basement membrane and neutrophil-rich infiltrates in histopathology. It can be seen both in children and adults. The form seen in children usually begins under the age of 5 and it is called chronic bullous disease of childhood. The classical presentation is annular/polycyclic plaques and papules with blistering on perioral and perineal regions, giving a "cluster of jewels" appearance. The adult form is often seen after the fourth decade and clinical features are similar to those of dermatitis herpetiformis, bullous pemphigoid or cicatricial pemphigoid.

Keywords: acquired epidermolysis bullosa, blisters, linear Ig A bullous dermatosis, subepidermal bullous diseases, linear IgA disease, chronic bullous dermatosis of chidhood

1. Acquired epidermolysis bullosa

1.1. Introduction

Acquired epidermolysis bullosa (AEB) is a chronic autoimmune subepidermal blistering disease characterized by autoantibodies to type VII collagen (C7), which is the main component of anchoring fibrils (AFs) [1, 2]. AEB patients have both tissue bound and circulating immunoglobulin (Ig)G autoantibodies targeting C7 [3]. AFs participate in attachment of epidermis and its underlying basement membrane zone (BMZ) to the dermis. It is thought that destruction of AFs due to autoantibodies targeting C7 results in a clinical phenotype of skin fragility, blisters, erosions, scars, milia and nail loss resembling genetic dystrophic epidermolysis bullosa [4]. Pathogenicity of these anti-C7 IgG antibodies is proved by demonstrating AEB-like blistering disease development in immunocompetent mice when human AEB antibodies were injected to them [5]. So, AEB results from an acquired autoimmune mechanism by which AFs can be compromised rather than by a gene defect as in hereditary dystrophic forms of epidermolysis bullosa (EB) [6].

AEB includes various clinical manifestations resembling dystrophic EB, bullous pemphigoid (BP), cicatricial pemphigoid (CP), Brunsting-Perry pemphigoid and linear immunoglobulin A bullous dermatosis (LABD) [7]. The diagnosis of AEB is often challenging because of these variety of clinical presentations. Evaluating patients only on the basis of clinical presentation and routine lesional histology is generally inadequate to distinguish AEB from other autoimmune subepidermal bullous diseases. Ancillary tests such as immunofluorescence, salt-split skin immunofluorescence (SSSI), transmission electron microscopy (TEM), immune electron microscopy (IEM), Western blot analysis, enzyme linked immunosorbent assay (ELISA) and fluorescent overlay antigen mapping (FOAM) are often necessary to confirm the diagnosis [8]. AEB is a chronic disease and often refractory to treatment but there have been developments in newer treatment modalities that have achieved some therapeutic success [9].

1.2. Historical aspects

AEB was initially described by G.T. Elliott in 1895 in two patients with acquired bullous disease reminiscent of EB who had no affected family members [10]. The term of "epidermolysis bullosa acquisita" was first coined by Kablitz in 1904 [11]. AEB was placed in the category of epidermolysis bullosa approximately 100 years ago because physicians were stuck by the similarity of clinical lesions seen in AEB patients and those seen in patients with hereditary dystrophic forms of EB [12]. In 1971, Roenigk et al. reviewed the AEB world literature and suggested the first diagnostic criteria for AEB: (1) spontaneous or trauma-induced blisters resembling hereditary dystrophic EB, (2) an adult onset of the disease, (3) a negative personal or family history for blistering disorder and (4) the exclusion of all other bullous diseases [13]. In 1980s, it was shown that patients with AEB had linear IgG deposits at their dermoepidermal junction (DEJ) detected by direct immunofluorescence. By IEM, it was demonstrated that the IgG immune deposits in AEB were localized below the lamina densa differently from BP [3, 14]. After that, in 1984, Woodley et al. identified 290-kDa and 145-kDa proteins

as the target antigen of AEB using serum samples from nine patients as a source of antibodies and concluded that AEB is a specific disease that is different from other primary bullous diseases [1]. This 290-kDa protein was later understood to be C7 [15]. A growing number of case reports about clinical presentations that are reminiscent of inflammatory BP, CP and Brunsting-Perry pemphigoid had reported in time [16–18].

1.3. Epidemiology and etiology

AEB is known as one of the rarest autoimmune blistering diseases with a incidence of approximately 0.17–0.5 per million people, per year and a prevalence of 2.84/million inhabitants [19–21]. The disease occurs at all ages but an epidemiological study of 30 Korean patients with AEB demonstrated the average age of onset of disease to be 44 years [22]. Children can also be affected [23]. No gender predisposition is known [21, 22]. AEB was found significantly more frequent in black patients in France. In the same study, there was a significant human leucocyte antigen (HLA)-DRB1*15:03 association with black patients from sub-Saharan Africa, suggesting a genetic predisposition to AEB in black patients of African origin [24].

The etiology of AEB is still unknown, but because the disease features IgG autoantibodies directed against C7, it is hypothesized that AEB may have an autoimmune pathogenesis [1, 2]. AEB is genetically associated with HLA-DR2; that is, HLA-DRB1*15 in black patients and HLA-DRB1*13 in Koreans [24–26]. HLA-DR2 phenotype has already been associated with hyperimmunity, which suggests an autoimmune etiology for AEB [25]. UV-radiation, vancomycin and contact allergy to metals have been reported as triggering factors of AEB in the literature [27, 28].

1.4. Pathophysiology

AEB is characterized by IgG autoantibodies directly attacking C7 within AFs [1, 2]. Although the precise role of autoantibodies against C7 in the pathogenesis of AEB is unclear, some clinical evidences support pathogenic role of antibodies to C7 in AEB. Blister formation in neonate of an AEB mother suggests that autoantibodies transferring from mother play a pathogenic role in inducing neonatal AEB [29].

Exact pathopysiological mechanism is unclear but it is very likely that AFs are essential for adherence of the epidermal layer of skin to the dermal layer. Because, the patients who are born with a defect in the gene that encodes for C7 exhibit skin fragility and skin blisters just like AEB patients due to the paucity of normal AFs [30].

AFs are specialized attachment complexes localized to the epithelium-mesenchyme interface in several tissues. AFs extend from the lower portion of dermoepidermal basement membrane to the underlying papillary dermis. They attach at both ends to the lamina densa, allowing entrapment of interstitial collagen fibers into U-shaped structures [31]. Ultrastructural studies of AEB skin have demonstrated a paucity of AFs [3, 14].

C7 is composed of three identical polypeptide alpha chains, coiled around each other to form triple helix configuration. Each alpha chain has 145-kDa central collagenous domain, characterized

by repeating Gly-X-Y amino acid sequences and a 39-amino acid non collagenous hinge region. The central domain is flanked by a large 145-kDa amino-terminal noncollagenous domain (NC1) and a smaller 34-kDa carboxyl-terminal noncollagenous domain (NC2) [32].

The amino-terminal (NC1) domain is approximately 145 kDa in size and consists of submodules with homology to adhesive proteins. NC1 includes a segment with homology to cartilage matrix protein (CMP), nine consecutive fibronectin type III-like repeats (FNIII), a segment with homology to the A domain of von Willebrand factor (VWF) and a short cysteine and proline-rich region [33, 34]. At the other end of the alpha chain, the carboxyl terminus, there is a much smaller non-collagenous globular domain called NC2, which is only 34 kDa [32]. The NC2 domain has a similar structure to the Kunitz protease inhibitor molecule [35].

Within the extracellular space, two C7 molecules align into antiparallel, tail-to-tail dimers. The carboxyl-terminal domains overlap between two C7 molecules, and the amino terminal domains present at the both ends of the molecule. Assembly of two C7 molecules is accompanied by proteolytic removal of a portion of the carboxy-terminal ends of both C7 molecules and stabilization by intermolecular disulfide bonding. Then, dimers aggregate laterally to form AFs, which are seen as semicircular loops in electron microscopy [36, 37].

NC1 interactions with several structural molecules of the BMZ such as type IV collagen, laminin-332, fibronectin and type I dermal collagen were demonstrated using recombinant NC1 expressed from human cells [35, 38, 39]. The seventh to ninth FNIII domains bind to laminin-322 [38] and vWF domain binds to type 1 collagen [40]. The NC1 domain has been shown to be the major antigenic portion of C7 in AEB using epitope mapping [41, 42]. It is suggested that autoantibodies directed against NC1 compromise the function of these adhesive proteins and lead to epidermal-dermal disadherence [6].

The results of several studies indicated that the autoimmune response is the key element in the pathogenesis of AEB. Gammon et al. demonstrated that sera from AEB patients induced leukocyte recruitment to the DEJ using a leukocyte attachment assay [43]. Sitaru et al. showed that sera from AEB patients induced dermal-epidermal separation in the cryosections of normal human skin, whereas sera from healthy controls did not [44].

Besides in vivo studies, animal models for AEB were developed. In the first successful passive AEB model, the disease could be induced in mice by injection of autoantibodies against murine C7 derived from immune rabbits [45]. In the active disease model, the clinical, histopathological and immunopathological findings in AEB patients were reproduced in mice by immunization with a recombinant fragment of the murine NC1 domain [46]. The latter served to investigate the loss of tolerance to C7. Further studies showed that complement activation and infiltration of granulocytes into the skin are essential for AEB induction in animal models [47, 48].

A number of studies have provided direct evidence that human AEB autoantibodies to NC1 domain of C7 are pathogenic and capable of inducing epidermal-dermal separation of skin. In one of them, affinity-purified anti-NC1 antibodies from AEB patients' sera were injected into adult immunocompetent hairless mice. The mice developed subepidermal bullous disease reminiscent of human AEB [5]. Woodley et al. demonstrated a small N-terminal 227 amino acids CMP homology domain as the first antigenic epitope on C7 proven to be a pathogenic target for AEB by passive transfer of autoantibodies from patients [49].

Subsequent evidences indicated the NC2 and the collagenous domains as to be minor targets for antibodies in AEB patients [50, 51]. Tissue-bound and circulating autoantibodies targeting the triple helical central domain of C7 were found in certain pediatric cases [52–54]. Minor antigenic epitopes localized to NC2 domain have also been demonstrated in recent reports [55]. AEB autoantibodies bound to NC2 domain may lead to epidermal-dermal disadherence by destabilizing AFs because of the role of NC2 and its adjacent collagenous segment in mediating antiparallel dimer formation of C7 [51]. As understood from these studies, AEB exhibits heterogeneous spectrum of autoantibody reactivities. But to date, there has been no evidence to indicate a correlation between epitope specificity of AEB autoantibodies and various clinicopathologic types [41, 56].

Analyses of the autoantibody response in AEB revealed the presence of IgG1 and IgG4 in the majority of patients [57, 58]. Complement-fixing IgG2a and IgG2b antibodies were detected in the basement membrane of AEB mouse models [46]. The Fc domains of IgG2a and IgG2b recruit neutrophils via Fc-gamma-RIV in the active mouse model. Inhibitor effect of Fc-gamma-RIIB and activator effect of Fc-gamma-RIV were demonstrated in the same study [59]. Complement factors are required for the blister formation in AEB, besides complement 5 (C5) knockout mice are resistant to blister development in a passive transfer mouse model [45]. T cells were proved to be required to produce blister-inducing antibodies in an active mouse model [60].

Development of inflammatory forms of AEB can be explained by the following sequential pathogenic scenarios: T cells stimulated by HLA-DR2 bearing antigen presenting cells that are presenting C7 subdomains. Activated T cells induce B cells and cause the production of C7 antibodies. These antibodies bind to epitopes on the NC1 domain of C7. The Fc domains of the antibodies activate complements and recruit neutrophils. C5a induces FcRIIIA upregulation and FcRIIB downregulation on neutrophils. C7 antibodies bind to Fc receptors and provide neutrophil activation. Reactive oxygen radicals, serine and metalloproteases that are produced by neutrophils mediate extracellular protein proteolysis. Blistering of mucocutaneous surfaces occurs as a consequence of the decrease in the amount of AFs [9, 35, 61, 62].

An experimental model for mechanobullous AEB has not been established yet so the pathomechanism of mechanobullous AEB is still unclear. But several possible mechanisms have been proposed [8]. It has been hypothesized that the normal interactions between NC1 and its extracellular matrix ligands such as laminin 5, fibronectin and type 4 collagen interrupted by autoantibodies may cause loss of the adherence of basement membrane and epidermis onto the papillary dermis [38]. Another potential mechanism behind mechanobullous disease is that AEB autoantibodies may interfere directly with the antiparallel dimer formation of C7 and anchoring fibril assembly [51].

1.5. Clinical manifestations

Two major clinical types of AEB are recognized: mechanobullous and inflammatory [35]. However, AEB classically presents as a mechanobullous disease, if the disease is defined as autoimmunity to C7 AEB can have clinical presentations that are reminiscent of inflammatory BP, CP and Brunsting-Perry pemphigoid [63]. A rare presentation of AEB is characterized by IgA autoantibodies to C7 [64].

There are five clinical presentations of AEB generally accepted: (1) classical presentation that is first reported and resembles the features seen in patients with inherited forms of DEB, (2) BP-like presentation, (3) CP-like presentation, (4) Brunsting-Perry pemphigoid–like presentation and (5) LABD-like disease [7, 63].

About two thirds of AEB patients present with one of the inflammatory variants. Some patients present with mixed phenotypes or in some, the clinical presentation may change during the course of the disease [65]. Kim et al. found no significant difference between mechanobullous and BP-like AEB with regard to sex, age of onset, oral involvement, treatment intensity or time to remission [22].

1.5.1. Classical AEB

This form is characterized by a mechanobullous disease with acral distribution [13]. Together with the BP-like AEB, classical AEB constitutes the majority of cases [22]. Milder forms of the disease are reminiscent of porphyria cutanea tarda, whereas its more severe forms are reminiscent of hereditary recessive dystrophic EB [14]. Patients present with skin fragility, trauma-induced blisters and erosions. Tense vesicles and bullae, which can be hemorrhagic, appear on non-inflamed or scarred skin [7]. Classical AEB is known to represent over trauma prone extensor surfaces such as back of the hands, knuckles, elbows, knees, sacral area and feet. Scaring reminiscent of hereditary dystrophic EB or porphyria cutanea tarda and pearl-like milia cysts frequently occur by healing of blisters [66]. Crusts, scales, scarring alopecia, nail dystrophy and postinflammatory pigment changes are other secondary lesions which result from healing of blisters and erosions. Involvement of the oral mucosa is prominent with erosions and superficial blisters [12, 62].

1.5.2. BP-like presentation

Although AEB classically presents as a non-inflammatory mechanobullous disease, it may manifests as widespread vesiculobullous lesions on inflamed skin reminiscent of BP [16]. It is the most common type of inflammatory AEB [22]. BP-like AEB manifests as widespread pruritic erythematous vesicobullous eruptions that can occur in any mucocutaneous localization [67]. The bullae are tense and localized on inflamed and/or urticarial skin of the trunk, extremities and skin folds [7]. In contrast to classical AEB, the distribution of the lesions is not confined to trauma-prone sites, skin fragility is not prominent and scarring and milia formation may be minimal or absent. Pruritus is frequent [8].

1.5.3. CP-like presentation

This form is characterized by a predominance of mucosal involvement and closely resemble CP [66]. Patients generally have erosions and scars of the mouth, upper esophagus, conjunctiva, nose, anus and genitals with or without similar lesions on the glabrous skin [68–70]. It can lead to the same complications of CP, including synechia, ankyloblepharon, blindness, nasal synechiae, laryngeal stenosis and dysphagia [71]. Tracheal involvement has also been reported [72]. Patients with the CP-like presentation often do not have trauma-induced lesions or skin fragility [35].

1.5.4. Brunsting-Perry pemphigoid-like presentation

Brunsting-Perry pemphigoid-like AEB presents with clinical features of Brunsting-Perry CP but results from autoimmunity to C7 [73]. Patients have chronic, recurrent subepidermal blisters with atrophic scars confined to the head, neck and upper aspect of the trunk with minimal or no mucosal involvement [74, 75].

1.5.5. LABD-like presentation

LABD-like AEB has common features with LABD, including subepidermal bullous eruption, neutrophilic infiltration and linear IgA deposition on the BMZ [35]. Autoantibodies of these patients are usually identified as IgA, IgG or both [8]. Onset of the disease is usually after third decade but may be in childhood too. Erythematous urticarial plaques, vesicles, bullae, erythema multiforme-like lesions and skin erosions may be seen. Pruritus is significant but scars and milium cysts are rare. Mucosal involvement is seen in 30% of the cases [71]. Ig-A mediated AEB can be defined as immunobullous disease with IgA localized at the level of the (sub)lamina densa zone as witnessed by indirect IEM or direct IEM or by a dermal BMZ staining pattern on salt-split skin. So, it is sufficient to separate this disorder from classic LABD using these immunophenotypic criteria [64].

1.5.6. Childhood AEB

Generalized and inflammatory LABD-like skin lesions and mucosal involvement is frequent in this rare form [76]. Callot-Mellot et al. reviewed 14 children with AEB, 5 of the patients presented with a LABD-like disease and 5 patients presented with the BP-like form of AEB. The classical form of AEB was seen in 4 children [77]. Mayuzumi et al. reviewed 33 children with AEB and reported that the inflammatory phenotype, mucosal involvement and favorable prognosis were more common in children than adult AEB patients. Autoantibodies in childhood AEB often target more than one domain of C7 [78].

1.6. Diagnostic methods

Diagnosing AEB based on the clinical picture and skin standard pathology is not possible because of the variety of clinical presentations [71]. Direct immunogold electron microscopy has been considered the gold standard of diagnosis [14]. But at present, diagnosis can be made by serration pattern analysis of direct immunofluorescence (DIF) microcopy and/or detection of serum autoantibodies against type C7 [79]. Linear deposits of IgG, IgA and/or complement 3 (C3) along the DEJ with an u-serrated pattern are diagnostic for AEB. Several test systems for the serological diagnosis of AEB have recently become available. Sophisticated diagnostic approaches only available in specialized centers are required in some patients [63].

1.6.1. Histopathology

Histopathology of a lesional skin biopsy helps to distinguish subepidermal blistering diseases from intraepidermal disorders. Initial histologic changes in the lesional skin are papillary edema

and vacuolar alteration along the DEJ that are followed by subepidermal cleft and blister at a later stage [12]. In the classical mechanobullous form, minimal or no inflammatory infiltrate is detected in dermis. In the inflammatory subtypes of AEB, infiltration of neutrophils with variable numbers of eosinophils, monocytes and lymphocytes are seen in the upper dermis [62, 80]. The infiltrate can be found around vessels, around follicles and in the interstitium. Fibrosis and milia formation are expected to be seen if cicatricial changes are present [12].

1.6.2. Transmission electron microscopy

Paucity of AFs and an amorphous, electron-dense band just beneath the lamina densa were demonstrated in the perilesional skin using electron microscopy [81] This finding could explain skin fragility by the similarity to that of EB hereditaria [82]. The cleavage plane of the blister does not indicate the diagnosis of AEB certainly. So, AEB cannot be differentiated from inherited epidermolysis bullosa and other pemphigoid disorders by TEM [63]. The cleavage may be seen either in the lamina lucida or the sublamina densa region [83]. Separation of the DEJ through the lamina lucida has been explained by the vulnerability of lamina lucida against proteolytic enzymes released during the inflammatory reaction at the BMZ [84]. The deeper level of separation in the classical form AEB may explain significant scar and milia formation, which is only rarely observed in the inflammatory type [85].

1.6.3. Immunoelectron microscopy

Direct IEM, which is approved as the diagnostic gold standard for AEB, allows to differentiate AEB from other pemphigoid diseases by visualizing the deposits of autoantibodies in the sublamina densa [3, 8]. IEM detects IgG autoantibodies at the lamina densa and sublamina densa of the BMZ, whereas IgG autoantibodies are localized to the upper lamina lucida in BP [7]. Direct IEM is performed to determine the ultrastructural localization of in vivo-bound IgG autoantibodies at the BMZ. Indirect IEM shows the binding site of circulating IgG autoantibodies at the BMZ [85]. Direct IEM is a sensitive diagnostic method, but it is a sophisticated procedure only available in few centers for the diagnosis of AEB [63].

1.6.4. Direct immunofluorescence

Immunofluorescence techniques maintain the pivotal role in the diagnostic algorithm of AEB. DIF on perilesional skin (with a radius of 1 cm) demonstrates linear binding of IgG and/or IgA, and/or C3 deposits along the dermal-epidermal junction [14, 63]. The deposition of multiple conjugates, including IgG, IgA, IgM, C3, complement 4 (C4) and properdin, is more frequently in AEB [85]. In LABD-like presentation, linear Ig A deposition presents without IgG [86].

BP has clinical and histopathological features, which may often be confused with AEB. DIF typically demonstrate linear deposition of IgG and C3 in the BMZ in both conditions [87]. Thus, salt split technique (SST) was introduced in 1984 to differentiate pemphigoid group from other subepidermal bullous diseases [88]. If skin samples are incubated in 1 M NaCl at 4°C for 24–72 hours, the epidermis can be pulled away from dermis with a fine forceps [6, 87–89].

Direct salt-split skin immunofluorescence can be used to distinguish AEB from BP. A routine DIF is performed on perilesional skin from patients who is fractured at the DEJ, through the lamina lucida zone. This cleavage places BP antigen on the epidermal side of the split, and other BMZ components including C7 on the dermal side. Therefore, if fluorescent label is observed along epidermal side of the salt-split skin, AEB is effectively excluded and the diagnosis of BP is suggested [8, 14]. But, this method is not sufficient to confirm AEB because anti-p200, protein-105 pemphigoid (Chan's disease) and anti-laminin-322 CP also show positive staining on the dermal side of the salt-split skin [7, 90–92].

Vodegel et al. demonstrated that IgG/IgA deposits at the BMZ can ultrastructurally be seen as upstanding arms between the rootlets of the basal keratinocytes, thus making u shapes [79]. U-serrated immunodeposition pattern in DIF is pathognomonic feature for AEB and bullous systemic lupus erythematosus (SLE), which are characterized with autoantibodies against C7 [65, 93]. Bullous SLE can be ruled out by other serologic and clinical criteria [7]. All other pemphigoid diseases show true linear or n-serrated pattern [93–95]. These patterns can be applied by DIF only. However, serration pattern may not be identified in mucosal biopsies and a number of skin samples [63, 96].

1.6.5. Indirect immunofluorescence (IIF)

IIF microscopy can be applied for detecting circulating antibodies. Standard substrates for this technique are monkey or rabbit esophagus as well as normal human skin. Incubation with 1 M NaCl solution of these substrates leads to cleavage within the lamina lucida [89]. So, IIF can also be done in salt-split skin with increased sensitivity [63]. Salt-split IIF allows to differentiate AEB from BP and LABD. Because AEB sera react on the dermal side (floor of the blister) of the salt-split skin, whereas BP and LABD sera react on the epidermal side (roof of the blister) [96]. A positive IIF result on the dermal side of the cleft does not make the diagnosis of AEB certain because dermal staining is also observed in patients with bullous SLE, anti-p200 pemphigoid, anti-epiligrin (laminin-332) CP and Chan's disease [7, 73, 90, 92, 97].

Another diagnostic method is IIF using substrate deficient in basement membrane molecules. C7-deficient skin from patients with dystrophic EB is required to perform this test. AEB sera does not show any labeling of skin deficient in C7, but linear fluorescence is seen at the BMZ on normal/salt-split human skin as well as on laminin-332–deficient skin [18, 73].

1.6.6. Western immunoblotting

Immunoblotting analyses are effective to confirm the diagnosis of AEB [8]. Dermal extracts from skin, amnion or cell culture are subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and electrophoretically transferred to a nitrocellulose membrane [12]. Recombinant forms of C7 can also be used [8]. When the membranes with immobilized proteins are incubated with AEB and control sera, AEB sera will be visualized by binding to a 290-kDa band, the alpha chain of C7, whereas control sera will not [8]. A second band of 145 kDa, which corresponds to NC1 domain of C7, will also be labeled with AEB antibodies [12]. Anti p-200 pemphigoid and AEB can be differentiated by Western blot. Patients' sera react with 200- and 290-kDa proteins in anti p-200 pemphigoid and AEB, respectively [62].

Although the sensitivity of immunoblotting is approximately 60%, using several recombinant proteins covering four immunodominant epitopes of NC1 domain increases to 80% [42].

1.6.7. Serology

Enzyme-linked immunosorbent assay (ELISA) demonstrates the presence of patient's circulating autoantibodies against specific basement membrane antigens [8]. AEB ELISAs have been developed using recombinant domains of C7, starting from the NC1 domain [35, 98]. The sensitivity and specificity of an ELISA system using NC1 domain were 94.5% and 98.7%, respectively, in the study of Komorowski et al. [99]. Recombinant NC1 and NC2 domains of C7 were also used in an ELISA system for AEB with sensitivity of 93.8% and specificity of 98.1% [100]. Autoantibodies to NC2 domain were detected in 20% of AEB patients by ELISA [71]. A positive correlation between ELISA values and disease severity of AEB patients was found in several studies [22, 101]. Compared to Western blotting and electron microscopy, ELISA is faster and easier to perform. ELISA method is also more sensitive because it detects autoantibodies that recognize the tertiary and quaternary structure of an antigen, whereas Western blotting only detects antibodies binding denatured, reduced proteins [8].

1.6.8. Fluorescence overlay antigen mapping

It is an efficient technique for identifying localization BMZ components and pathogenic antibodies on perilesional skin from patients with autoimmune diseases [8]. The skin samples are subjected to co-incubation with monoclonal antibodies against human IgG and type VII collagen separately and then stained with different fluorescent stains. Computer-aided superposition of the fluorescent-stained images allows to detect IgG deposits, which can be above (BP) or at the same location of C7 (AEB) [102].

1.7. Diagnosis

In a patient with clinical picture compatible with AEB, the initial and the gold standard diagnostic test is DIF microscopy including serration pattern analyses (u-serrated: AEB, n-serrated: other subepidermal diseases). When IgG/IgA/C3 along the DEJ is observed without a serration pattern, IIF microscopy on human salt-split is the next diagnostic procedure. IgA/IgG at the epidermal side refers to the diagnosis of BP, CP or LABD.

If IIF microscopy is negative or IgA/IgG at the dermal side of the split is detected, then C7-specific ELISA or IIF (Euroimmun, MBL) should be performed (even when diagnosis of AEB has been established by pattern analysis of DIF or direct IEM, serum should be analyzed for autoantibodies against C7). Immunoblotting, IIF microscopy on C7 deficient skin, FOAM and direct IEM are the next diagnostic tools (depending on availability), in case of negative ELISA result. Positivity in any of the four assays will allow diagnosis of AEB [63].

1.8. Differential diagnosis

BP is characterized by predominant IgG reactivity by DIF and/or IIF microscopy, no floor binding by IIF microscopy and no predominant mucosal involvement. CP presents with

predominant mucosal involvement. When floor binding is detected by IIF microscopy, laminin-332 reactivity needs to be analyzed. LABD shows predominant IgA reactivity by DIF and/or IIF microscopy. Anti-p200 pemphigoid is characterized by reactivity with the p-200 protein and/or laminin $\gamma 1$ [63].

1.9. The relationship between AEB and other systemic diseases

A variety of other diseases were reported to be coexisting with AEB [12]. Inflammatory bowel diseases, especially Crohn's disease, is the most common disorder associated with AEB [103]. While in the United States, 25% of AEB patients also have inflammatory bowel disease; this association is not found in Korean patients [22, 104]. Rheumatoid arthritis, diabetes, cryoglobulinemia, psoriasis and hematological malignancies were also reported to be associated with AEB in anecdotal reports [105–107].

1.10. Treatment

Management of AEB is challenging, because noninflammatory mechanobullous form is often refractory to treatment, and the inflammatory forms may require the use of high-dose corticosteroids combined with other immunosuppressants resulting in increased morbidity [62]. All patients need supportive therapy to help reduce risk of complications of AEB. Education for avoiding trauma and wound management improve their quality of life [12]. The most widely used medication for treatment of AEB is systemic corticosteroids but the outcome is usually poor. Mild clinical features respond well to low-dose (05–1 mg/kg/day) corticosteroid therapy, whereas high-dose (1–1.5 mg/kg/day) corticosteroid therapy is mandatory in some patients [62].

Colchicine (2 mg/day) has been reported to be effective in patients with both classical and inflammatory presentations probably by the mechanism of inhibiting antigen presentation to T cells [108]. The side effect profile of colchicine is relatively benign so it is often used as a first-line drug alone or combined with corticosteroids [62]. Dapson (25–100 mg/day) is also effective in some patients, especially when neutrophils are present in their dermal infiltration [109].

Because of the unsatisfactory outcome and extensive side effects of systemic corticosteroids, immunosuppressive agents are required as adjuvant regimens [62]. Although a number of patients have been reported to respond to cyclosporine therapy (>6 mg/kg/day), the use of cyclosporine is limited due to the long-term toxicity of the drug [110]. In intractable cases, it is recommended to use cyclosporine (3–60 mg/kg/day) in addition to corticosteroids [62].

Mycophenolate mofetil (1–2 g/day), methotrexate (7.5 mg/week), and pulse cyclophosphamide (500 mg for 1 day) can be used for their steroid-sparing effects in patients with inflammatory forms. The effectiveness of these agents is varied among patients [62].

Intravenous immunoglobulin G (IVIG) has been used successfully in some severe refractory AEB patients. IVIG has the advantage of lacking immunosuppression [111]. It is recommended for patients not responding to conventional therapy [62]. Rituximab decreases the number of circulating B cells, plasma cells and amount of antibody production. It was used successfully in a small number of severe and refractory patients [35, 112]. Plasmapheresis, immunoadsorption and photopheresis are other therapeutic modalities; however, the experience of using

them in AEB is fairly limited [8, 35]. Infliximab is considered to be an alternative treatment of patients with AEB in future [35]. In a study conducted by Le Roux-Villet et al., 206 articles were analyzed; it was emphasized that only two were of an adequate level of proof, with four of intermediate level and all the others of only low level. Therefore, it is difficult to suggest optimal treatment. Further data are needed to establish the optimal treatment approach [113].

2. Linear immunoglobulin A bullous dermatosis

2.1. Introduction

LABD, also known as Linear IgA disease, is a rare autoimmune subepidermal bullous disease affecting adults and children, which is characterized by the linear deposits of IgA antibodies in BMZ [114, 115]. LABD is usually idiopathic, but medications, malignancies and infections may play a role in the etiology of LABD. The primary implicated agent is vancomycin [116]. In the adult-onset form, arcuate or linear tense vesicles and bullae arising on urticarial looking plaques or normal skin localize on the extensor surfaces [115]. Childhood-onset LABD, which is historically known as chronic bullous dermatosis of childhood (CBDC), represents the most common autoimmune bullous disease among children [117]. The childhood-onset form of LABD has a slightly different presentation with perioral, periorbital, genital and lower limb localization. Annular polycyclic "string-of-pearls" sign is more common in the childhood form [115]. Target antigens of circulating antibodies exhibit heterogeneous features as well as the clinical presentations. LABD is immune serologically divided into two subgroups according to the reaction with the epidermal/dermal sides of 1 mol L NaCl-split normal human skin in IIF [118]. In the lamina lucida-type LABD, the major target antigens are the 120-kDa LAD-1 antigen and its carboxyterminal proteolysed form 97-kDa LABD97 antigen. In the sublamina densa-type LABD, the splitting level is deeper and the target antigen is C7 [117, 119]. Other certain incriminated antigens are BP230, BP180 NC16a domain, 285-kDa antigen, laminin-332 and 200-kDa laminin $\gamma 1$ [120]. Autoimmune diseases (post-streptococcal glomerulonephritis), inflammatory bowel disease (ulcerative colitis) and lymphoproliferative disorders were reported to trigger LABD with an unknown mechanism [121]. Skin lesions respond rapidly to dapsone or sulfapyridine treatment [122].

2.2. Historical aspect

LABD was firstly described in children with nonpruritic mucocutaneous blisters misdiagnosed as dermatitis herpetiformis (DH) [123]. Subsequent patients were called "bullous pemphigoid of childhood," "childhood DH" and finally "chronic bullous dermatosis of childhood" by other clinicians [124]. After that, continuous linear deposits of IgA along the BMZ were showed [125]. Currently, it is known as the childhood counterpart of LABD [114].

2.3. Epidemiology

Reported incidence rates were 0.23/million/year in Germany [126], 0.49/million/year in France [19] and 2.3/million/year in Kuwait [127]. Interestingly, LABD was reported to be more frequent

in Uganda [128], South Africa [129], Mali [130] and Tunus [131]. This may be explained with the variation of age distribution in these countries compared to others. No racial or gender predilection has been reported [132]. LABD can affect all ages, but two peaks have been frequently observed: childhood onset and adult onset [133]. The childhood-onset form usually appears between 6 months and 5–6 years of age. Spontaneous remission may occur within 5 years or it may persist until puberty. On the other hand, the adult-onset form generally appears after the sixth decade and tends to be more chronic [114, 117]. Neonatal cases are extremely rare [134].

2.4. Etiology

Several studies were carried out to assess the possible effect of genetic predisposition for LABD. Collier et al. showed an increased frequency of HLA Cw7, B8, DR3, DQ2 and tumor necrosis factor (TNF2) alleles. Genetic association of HLA-Cw7, HLA-B8 and HLA-DR3 with LABD was reported especially in childhood form rather than the adult form. TNF2 allele was associated with worse prognosis in both children and adult groups [135]. HLA-B8 haplotype was found to be related with favorable prognosis [136].

Although LABD is mostly idiopathic, there are several precipitating factors, such as drugs, infections and malignancies, and traumatic events, such as burns and ultraviolet light exposure [114, 117]. Intake of certain drugs, most commonly vancomycin [137], has been implicated as the causal agent. In addition to this, over 20 other medications have been suspected as potential triggers in case reports [138–142]. (**Table 1**) Drug-related cases are responsible from 37.5% of adult patients [115]. It is possible that these drugs cross-react with autoantigens of the BMZ by changing their conformational structure or unmasking previously hidden antigens to the immune system [143].

Antimicrobials	**Ace inhibitors/angiotensin receptor blockers**	**Antiepileptics**
Vancomycin	Captopril	Phenytoin
Penicillin	Eprosartan	Carbamazepine
Cephalosporins	Candesartan	Vigabatrin
Sulfonamide	**Antiarrhythmics**	**Antidiabetics**
Piperacillin-tazobactam	Amiodarone	Glibenclamide
Rifampin	Verapamil	Glyburide
Imipenem	**Immunomodulating agents**	**Miscellaneous drugs**
Nonsteroidal anti-inflammatory drugs	Cyclosporine	Atorvastatin
Diclofenac	Ustekinumab	Furosemide
Naproxen	Infliximab	Lithium carbonate
Piroxicam	Granulocyte colony-stimulating factor	Somatostatin
Ketoprofen	Interferon-α,γ	Gemcitabine
Oxaprozin	Interleukin-2	

Table 1. Medications associated with drug-induced LABD.

LABD has been associated with lymphoproliferative malignancies, especially non-Hodgkin lymphoma and Hodgkin lymphoma [144]. Besides, association with solid organ malignancies has also been reported, including bladder, esophagus, breast, uterus, colon and thyroid carcinoma [145–147]. There are documented two LABD cases, which occur after influenza and human papillomavirus vaccination [148]. Additionally, LABD is triggered by upper respiratory infections, varicella zoster virus and antibiotic-treated tetanus infections. Perhaps infectious agents may play a role in the development of autoimmune response [149, 150].

Inflammatory bowel diseases, mainly ulcerative colitis, are the most common diseases associated with LABD. The chronic inflammation in the gastrointestinal tract is thought to be responsible in abnormal IgA production. The cross-reaction of colonic epithelial cells and cutaneous BMZ antigens may be related to this coexistence [151]. Although a definite association is yet to be established, LABD has also been reported with primary amyloidosis [152], interstitial pneumonia [153], rheumatoid arthritis [154], SLE [155] and glomerulonephritis (**Table 2**) [156].

Lymphoproliferative malignancies
Non-Hodgkin lymphoma
Hodgkin lymphoma
Solid organ malignancies
Bladder, esophagus, breast, uterus, colon and thyroid carcinoma
Inflammatory bowel diseases
Ulcerative colitis
Crohn's disease
Primary amyloidosis
Interstitial pneumonia
Rheumatoid arthritis
SLE
Glomerulonephritis

Table 2. Disorders associated with LABD.

2.5. Pathogenesis

Linear IgA disease is a subepidermal immunobullous disease characterized by IgA autoantibodies directed against several antigens located in the BMZ of the skin and mucosal tissues lined with stratified squamous epithelia. Despite many studies over several decades, the pathophysiologic mechanism that triggers the autoimmune response in LABD still

needs to be better clarified [114]. Target antigens of circulating autoantibodies are classified into two groups, those residing in lamina lucida and those in sublamina densa. From this point of view, LABD is divided into two subgroups, lamina lucida-type and sublamina densa-type [157, 158].

Using 1 mol L NaCl-split normal human skin as a substrate for IIF, the majority of the patients' sera shows epidermal binding, which implies an antigen associated with hemidesmosomes or the upper lamina lucida, and a minority of those bind to the dermal aspect of the artificial blister suggests a lower lamina lucida or dermal antigen. However, some patients' sera show reactivity to both epidermal and dermal sides (mixed type) [159]. In patients with lamina lucida-type LABD, IgA autoantibodies react most frequently with the 97-kDa protein (LABD-97) and 120-kDa protein (LAD-1) [160, 161]. These two most common LABD antigens are fragments of BP180 ectodomain [162, 163].

BP180, or collagen XVII, is a transmembrane hemidesmosome-associated protein with an extracellular collagenous domain spanning the lamina lucida [164]. The extracellular domain of BP180/collagen XVII molecule is partly shed and is further fragmented by proteolytic action into neoepitopes [162]. The LAD-1 is generated when collagen XVII is cleaved by keratinocyte metalloproteinases, ADAM-9 and 10 [165]. This cleavage is just in the noncollagenous (NC)16A domain of the BP180, and this explains that 20% of the sera of LABD patients react with the NC16A domain [117, 166]. NC16A domain, which is the major pathogenic epitope in the extracellular domain of BP180 in BP, is also a target for IgA antibodies in LABD, frequently in conjunction with other antigenic targets [167]. LABD97 is cleaved from NC16 domain of collagen XVII as well as LAD1, and further C-terminal processing of LAD1 induces LABD-97 [168, 169]. IgA antibodies to 290-kDa antigen (C7) and 255-kDa dermal antigen are most frequently detected in patients with sublamina densa-type LABD [170, 171]. Tsuchisaka et al. demonstrated that C7 is the major autoantigen for sublamina densa-type LABD [119]. A 285-kDa antigen (LAD285) has been found in patients whose sera have both dermal and epidermal binding on immunofluorescence testing using split skin [172, 173]. LAD285 is thought to be the immunodominant dermal-associated antigen, which represent the site of the original antibody attack in patients with a response to dermal and epidermal antigens [173]. The full-length BP180, BP230, laminin-332, laminin $\gamma 1$ and $\alpha 6\beta 4$ integrin are less common antigenic targets of IgA [174–176].

Most of the patients' sera have more than 1 target antigen suggesting that there is a primary disease-provoking epitope with spread of the immune response to other epitopes on the same or adjacent molecules. It is also demonstrated that the phenomenon of intermolecular epitope spreading is common, age dependent in LABD and is associated with IgA antibodies rather than IgG antibodies [173].

The pathogenesis involves IgA and less frequently IgG autoantibodies directed against BMZ antigens [172]. Previous investigations have demonstrated that A1 subclass is responsible for development of the disease [177]. IgA is a chemoattractant of neutrophilic granulocytes. Antigen-antibody binding leads to complement activation, predominantly neutrophilic inflammatory infiltration and proteolysis mainly occurs through the cooperation of

neutrophil elastase and MMP-9/gelatinase B that result in tissue injury and blister formation [114, 142, 178, 179]. There is indirect evidence for the pathogenicity of the IgA antibodies. A recent research has demonstrated that transfer of monoclonal IgA antibodies against the 97-kDa LAD antigen into severe combined immunodeficient mice with human skin grafts resulted in IgA deposits along the BMZ, recruitment of neutrophils, and subepidermal vesicle formation [180].

2.6. Clinical features

Clinical manifestations of LABD are heterogenous and often resemble those of BP and DH. Characteristic clinical features are tense vesicles and/or bullae on the normal/erythematous/urticarial base [181].

These lesions may occur in various size and form as annular or polycystic plaques. As referred before, there are two forms of LABD: adult onset and childhood onset (CBDC). The distribution of the lesions differs in these two forms.

Lesions in CBDC mostly occur in the lower abdomen and anogenital areas, with a frequent involvement of the perineum and less often perioral area. New lesions appear in the periphery of older ones, named as "cluster of jewels." The localization in the lower abdomen and the anogenital region is typical for childhood form. Patients complain of severe itching and burning and rupture of blisters may develop secondary infections [114, 182].

In adults, there may be several clinical manifestations such as papular, vesicular, bullous, erythematous and edematous lesions that localized on extensor surfaces, including trunk and buttocks. Erythema multiforme-like, prurigo nodularis-like [183] and contact dermatitis-like lesions [184] may occur. These lesions may distribute symmetrically or asymmetrically in both child and adult forms. It is difficult to distinguish disease from DH especially in the presence of symmetrical excoriated pruritic papules. LABD should be considered when the annular lesions are present. Larger bullae can be seen in some patients with BP or AEB. Histopathological and serological examinations should be performed to differentiate LABD from all these diseases [181, 185].

Oral mucosa and ocular surface are the most common locations in LABD [186]. Larynx, pharynx, trachea, esophagus and vaginal mucosa may be affected. The involvement of oral mucosa occurs in 60–70% of LABD patients. It is more common in adults. These mucosal lesions may be the only clinical manifestation in truly minority of patients. Painful erosions or ulcers or desquamative gingivitis may occur in oral mucosa [187, 188]. Ocular lesions heal with scar just like CP. Ocular findings include dry eye, foreign body sensation, entropion, conjunctival scarring with trichiasis, corneal opacification, neovascularization and potential blindness [189].

Recent case series demonstrated that the course of drug-induced LABD is atypical and more severe compared to the idiopathic form. Lesions usually occur within 5 to 26 days

(median 10 days) after drug intake and usually resolve within 4 weeks after drug withdrawal. But exceptional cases may persist for months. Vancomycin is the most commonly prescribed drug. Drug-induced LABD may clinically resemble toxic epidermal necrolysis with large erosions and positive Nikolsky sign [190, 191]. Morbilliform and localized palmar variants have been defined and the responsible drug in these variants is usually vancomycin [192, 193].

2.7. Diagnosis

The diagnosis of LABD is based on clinical, histopathologic and immunologic parameters [114]. Routine histopathology of the lesional skin classically shows subepithelial blister formation with a diffuse underlying neutrophilic infiltrate in the dermis accompanying mononuclear cells and eosinophils. These findings are identical to those of DH [194]. But neutrophils are usually much less diffuse and are more common in papillary tips in DH [116]. These findings can be observed in other subepidermal blistering diseases such as BP and AEB [195].

Owing to the fact that clinical and histologic features of LABD are frequently overlap with those of other subepidermal bullous diseases, it is essential to verify the presence of IgA autoantibodies using at least one of the immunopathologic examinations, including DIF, IIF, Western immunoblotting or IEM [114]. The gold standard test for diagnosis of LABD is DIF microscopy of perilesional, clinically normal-appearing skin or mucous membrane that reveals linear IgA deposits along the BMZ [196]. The forearm is not a suitable biopsy site, as antigen expression is detected to be insufficient [197]. In cases of lamina lucida-type of LAD, immunofluorescence analysis of perilesional skin biopsies show linear Ig A deposits that have n-serrated pattern in contrast to sublamina densa-type LAD where the deposits have an u-serrated pattern [117]. Deposition of IgG, IgM, or C3 in conjunction with IgA may be seen in some cases [114]. The presence of linear IgG deposition in addition to IgA along the BMZ has provoked some controversy [116]. In some cases of DH, the pattern of the IgA deposition may be linear. So, it might be necessary to use another confirmatory immunologic test for distinguishing DH from LABD [198].

Serum and, rarely, blister fluid are used for IIF to detect circulating IgA antibodies [199]. IIF shows a variable positivity of 30–50% of LABD patients and tends to be more positive in children (≥75%) than in adults (30%) [133, 182, 200]. As the low circulating autoantibody titers make difficult to detect positivity, it should be done on salt-split human skin for increased sensitivity [201]. IgA deposits can be detected on epidermal, dermal or both sides of the salt-split skin by IIF. In most cases, sera of the patients show epidermal bindings (lamina lucida-type LABD) [159]. Sublamina densa-type LAD accounts for the minority of the patients and shows dermal binding [202]. Some cases show a mixed pattern [203]. IIF on salt-split skin is usually negative in drug-induced LABD [191].

IEM is a specific diagnostic tool, which detects the exact location of immune deposits but it is expensive and only used by small numbers of centers [114]. By direct IEM, the IgA deposits

were found in lamina lucida, basal surface of hemidesmosomes, lamina densa and sublamina densa region [204]. "Mirror image" is defined as the IEM finding of several cases in which the immune deposits are located at the both sides of lamina densa [205].

Western blot is not commonly used because it is time-consuming, expensive and not feasible in most centers [116]. But multiple target antigens have been identified by the Western blot analysis within last 20 years [114]. It is a sensitive method for detecting IgA antibodies against LABD97 and LAD-1 [117, 172]. Remaining recognized antigens, including BP180, BP230 and C7 that are shared by other subepidermal bullous diseases, make the diagnosis more challenging [114]. When the mentioned methods do not provide information, Western blot analysis can enable to reach an accurate diagnosis [206].

2.8. Differential diagnosis

Clinically, LABD can resemble other blistering disorders such as BP, DH, AEB, CP and bullous SLE [114]. BP is characterized by linear deposition in the BMZ of IgG and C3 while immunofluorescence studies for DH demonstrate granular IgA deposits in the dermal papillae [207]. Cases reported to show IgA autoantibodies to the 290-kDa C7 may be diagnosed as sublamina densa-type LABD or IgA-mediated AEB. However, other clinical characteristics, such as milia and atrophic scarring, can be used to differentiate AEB from LABD [208]. LABD with predominant mucosal involvement can mimic CP clinically, but differentiates by immunofluorescence findings from other bullous diseases.

Salt split-skin immunofluorescence assays demonstrate that both circulating and tissue-fixed IgA autoantibodies mostly deposit on the roof of the split in LABD. In CP, antibodies are seen on the floor or roof of the split [209]. AEB is always recognized by dermal deposits. In LABD patients' sera, autoantibodies are mainly against 97- or 120-kDa antigens, whereas autoantibodies in BP patients target 180 and/or 230 kDa antigens [210]. Circulating and tissue-bound antibodies target 180-kDa or laminin-322 in CP patients [209] and 145- or 290-kDa antigens in AEB patients [64].

Although several authors have suggested their own criteria, there is no diagnostic guideline or consensus about LABD [116]. Some investigators suggest that solely linear IgA deposition with no other immunoglobulins or complement deposition at the BMZ in DIF is essential [202]. However, others proposed that prominent linear IgA deposition at the BMZ, irrespective of concurrent weak IgG deposition, is consistent with a diagnosis of LABD [211, 212]. Moreover, IF staining intensity depends on the experimental conditions, such as dilution and the type of second step antibodies. Thus, it is often difficult to assess predominance [116]. Several cases of subepidermal blistering diseases including BP, CP and AEB with linear IgA deposits reported previously point to the complicated immunopathological features of these disease spectrums [213–215].

In minority of the cases, circulating IgG anti-BMZ antibodies can be detected and deposition of linear IgG may be seen by DIF parallel to IgA although in less intensity [158]. A Japanese review of 213 patients with LABD found both IgA and IgG anti-BMZ antibodies in approximately 20% of the cases [216]. Therefore, several authors consider them to be overlap syndromes and

prefer the designation of linear IgA/IgG bullous dermatosis (LAGBD) [120, 194, 208]. LAGBD comprises a heterogeneous group of diseases, and most cases show pruritic vesiculobullous eruptions similar to those of LABD [212].

2.9. Treatment

The involvement site and the severity of the disease should be considered for treatment choice. Potent topical corticosteroids (clobetasol propionate) may be effective in mild disease [217]. The possibility of a drug effect or an association with underlying malignancy or bowel disease should be evaluated because discontinuation of the offending drug or treating the underlying disease may produce a remission. If there is no evidence of an associated medication or disease, dapson is the drug of choice for the initial treatment of patients with LABD [194]. Many cases often respond dramatically within 24–48 hours to dapsone. It is used in doses of 50–200 mg/day. Prednisolone (0.5–2 mg/kg/d) treatment may be added in cases with dapson resistance [114]. When there is intolerance to dapson or inadequate response, alternative treatments with sulfapyridine, colchicine, tetracycline and niacinamide, mycophenolate, azathioprine or rituximab should be considered [194]. In case of ocular disease, rituximab is indicated in patients with dapson resistance [218]. Cyclophosphamide or other immunosuppressants are the next options [194].

In general, same drug regimens can be used for both children and adults, but dose adjustment is required in children. Legendre et al. have used botulinum toxin A for LABD located in the axillae and observed a decrease in severity of symptoms [219]. Although treatment-discontinuation modalities were not investigated, it is commonly accepted that treatment should not be ended before DIF becomes negative in skin with a previously positive lesion site [174].

2.10. Prognosis

The natural course of the disease cannot be estimated precisely because of the rare occurrence of LABD and the inadequate long-term follow-up of patients. According to Gottlieb study, it is achieved that one-third of patients had complete remission. One-third of the patients had chronic disease and the other one-third had relapses. Major risk factors for chronic disease are mucosal involvement, age over 70 years and pure linear IgA deposits at the BMZ. Mucosal lesions are more resistant to treatment and may lead to stricture formation or conjunctival and corneal scarring [174].

The clinical course of CBDC is mild, and mucosal involvement is less common than adult form [131]. CBDC is self-limited disease. The average duration of the disease is 3–4 years, but it may be longer in some patients.

3. Conclusion

To conclude, AEB and LABD are distinct autoimmune blistering diseases with various subtypes some of which share overlapping clinical and immunohistopathologic features. No

histologic features differentiate LABD from AEB or other subepidermal bullous diseases. Immunofluorescence microscopy is mandatory for diagnosis. However, diagnosis and management of these diseases still remain challenging because of the polymorphous clinical picture, sophisticated diagnostic approach and lack of prospective controlled clinical trials. Future studies are required to clarify the exact role of numerous basal membrane antigens/epitopes, border lines between overlapping autoimmune bullous diseases and new therapeutic options.

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References

[1] Woodley DT, Briggaman RA, O'Keefe EJ, et al. Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. The New England Journal of Medicine. 1984 Apr 19;**310**(16):1007-1013. DOI: 10.1056/NEJM198404193101602

[2] Woodley DT, Burgeson RE, Lunstrum G, et al. Epidermolysis bullosa acquisita antigen is the globular carboxyl terminus of type VII procollagen. The Journal of Clinical Investigation. 1988 Mar;**81**(3):683-687. DOI: 0.1172/JCI113373

[3] Nieboer C, Boorsma DM, Woerdeman MJ. Immunoelectron microscopic findings in cicatricial pemphigoid: Their significance in relation to epidermolysis bullosa acquisita. The British Journal of Dermatology. 1982 Apr;**106**(4):419-421. DOI: 10.1111/j.1365-2133.1982.tb04534.x

[4] Woodley DT, Chang C, Saadat P, et al. Evidence that anti-typeVII collagen antibodies are pathogenic and responsible for the clinical, histological, and immunological features of epidermolysis bullosa acquisita. The Journal of Investigative Dermatology. 2005 May;**124**(5):958-964. DOI: 10.1111/j.0022-202X.2005.23702.x

[5] Woodley DT, Ram R, Doostan A, et al. Induction of epidermolysis bullosa acquisita in mice by passive transfer of autoantibodies from patients. The Journal of Investigative Dermatology. 2006;**126**(6):1323-1330. PubMed PMID: 16543893. DOI: 10.1038/sj.jid.5700254

[6] Chen M, Hallel-Halevy D, Nadelman C, Woodley DT. Epidermolysis Bullosa Acquisita. Autoimmune Diseases of the Skin. Wien, New York: Springer; 2005. pp. 109-132. DOI: 10.1007/b139016

[7] Remington J, Chen M, Burne J, Woodley DT. Autoimmunity to Type VII Collagen: Epidermolysis Bullosa Acquisita. Dermatologic Immunity. Basel: Karger Publishers; 2008. pp. 195-205. DOI: 10.1159/000131455

[8] Chen M, Kim GH, Prakash L, et al. Epidermolysis bullosa acquisita: Autoimmunity to anchoring fibril collagen. Autoimmunity. 2012 Feb;**45**(1):91-101. DOI: 10.3109/0891 6934.2011.606450

[9] Kasperkiewicz M, Sadik CD, Bieber K, et al. Epidermolysis bullosa acquisita: From pathophysiology to novel therapeutic options. The Journal of Investigative Dermatology. 2016 Jan;**136**(1):24-33. DOI: 10.1038/JID.2015.356

[10] Savill AF. Two cases of epidermolysis bullosa. The Lancet, 1906;**168**(4324):86-88. DOI: https://doi.org/10.1016/S0140-6736(01)32585-0

[11] Pass F, Dobson RL. Epidermolysis Bullosa Acquisita a disease of dermal connective tissue. Archives of Dermatology. 1965;**91**(3):219-223. DOI: 10.1001/archderm.1965. 01600090027004

[12] Gupta R, Woodley DT, Chen M. Epidermolysis bullosa acquisita. Clinics in Dermatology. 2012;**30**(1):60-69. DOI: 10.1016/j.clindermatol.2011.03.011

[13] Roenigk HH Jr, Ryan JG, Bergfeld WF. Epidermolysis bullosa acquisita. Report of three cases and review of all published cases. Archives of Dermatology 1971;**103**(1):1-10. doi:10.1001/archderm.1971.04000130003001

[14] Yaoita H, Briggaman RA, Lawley TJ, et al. Epidermolysis bullosa acquisita: Ultrastructural and immunological studies. The Journal of Investigative Dermatology. 1981 Apr;**76**(4):288-292. DOI: 10.1111/1523-1747.ep12526124

[15] Woodley DT, Briggaman RA, Gammon WR. Acquired epidermolysis bullosa. A bullous disease associated with autoimmunity to type VII (anchoring fibril) collagen. Dermatologic Clinics. 1990 Oct;**8**(4):717-726 2249362

[16] Gammon WR, Briggaman RA, Wheeler CE Jr. Epidermolysis bullosa acquisita presenting as an inflammatory bullous disease. Journal of the American Academy of Dermatology. 1982 Sep;**7**(3):382-387 DOI: 10.1016/S0190-9622(82)80319-8

[17] Tokuda Y, Amagai M, Yaoita H, et al. A case of an inflammatory variant of epidermolysis bullosa acquisita: Chronic bullous dermatosis associated with nonscarring mucosal blisters and circulating IgG anti-type-VII-collagen antibody. Dermatology. 1998;**197**(1):58-61. DOI: 10.1159/000017958

[18] Jonkman MF, Schuur J, Dijk F, et al. Inflammatory variant of epidermolysis bullosa acquisita with IgG autoantibodies against type VII collagen and laminin alpha3. Archives of Dermatology. 2000 Feb;**136**(2):227-231. DOI: 10.1001/archderm.136.2.227

[19] Bernard P, Vaillant L, Labeille B, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous diseases French study group. Archives of Dermatology. 1995 Jan;**131**(1):48-52. DOI: 10.1001/arch-derm.1995. 01690130050009

[20] Bertram F, Bröcker EB, Zillikens D, et al. Prospective analysis of the incidence of autoimmune bullous disorders in lower Franconia, Germany. Journal der Deutschen Dermatologischen Gesellschaft. 2009 May;**7**(5):434-440. DOI: 10.1111/j.1610-0387.2008.06976.x

[21] Hübner F, Recke A, Zillikens D, et al. Prevalence and age distribution of pemphigus and Pemphigoid diseases in Germany. The Journal of Investigative Dermatology. 2016 Dec;**136**(12):2495-2498. DOI: 10.1016/j.jid.2016.07.01

[22] Kim JH, Kim YH, Kim SC. Epidermolysis bullosa acquisita: A retrospective clinical analysis of 30 cases. Acta Dermato-Venereologica. 2011 May;**91**(3):307-312. DOI: 10.2340/00015555-1065

[23] Arpey CJ, Elewski BE, Moritz DK, et al. Childhood epidermolysis bullosa acquisita. Report of three cases and review of literature. Journal of the American Academy of Dermatology. 1991 May;**24**(5 Pt 1):706-714. DOI: 10.1016/j.jid.2016.07.013

[24] Zumelzu C, Le Roux-Villet C, Loiseau P, et al. Black patients of African descent and HLA-DRB1*15:03 frequency overrepresented in epidermolysis bullosa acquisita. The Journal of Investigative Dermatology. 2011 Dec;**131**(12):2386-2393. DOI: 10.1038/jid.2011.231

[25] Gammon WR, Heise ER, Burke WA, et al. Increased frequency of HLA-DR2 in patients with autoantibodies to epidermolysis bullosa acquisita antigen: Evidence that the expression of autoimmunity to type VII collagen is HLA class II allele associated. The Journal of Investigative Dermatology. 1988 Sep;**91**(3):228-232. DOI: 10.1111/1523-1747.ep12470317

[26] Lee CW, Kim SC, Han H. Distribution of HLA class II alleles in Korean patients with epidermolysis bullosa acquisita. Dermatology. 1996;**193**(4):328-329. DOI: 10.1159/000246282

[27] Jappe U, Zillikens D, Bonnekoh B, et al. Epidermolysis bullosa acquisita with ultraviolet radiationsensitivity. The British Journal of Dermatology. 2000 Mar;**142**(3):517-520. DOI: 10.1046/j.1365-2133.2000.03368.x

[28] Delbaldo C, Chen M, Friedli A, et al. Drug-induced epidermolysis bullosa acquisita with antibodies to type VII collagen. Journal of the American Academy of Dermatology. 2002 May;**46**(5 Suppl):S161-S164. DOI: 10.1067/mjd.2002.107774

[29] Abrams ML, Smidt A, Benjamin L, Chen M, Woodley D, Mancini AJ. Congenital epidermolysis bullosa acquisita: vertical transfer of maternal autoantibody from mother to infant. Archives of dermatology. 2011;**147**(3):337-341. DOI: 10.1001/archdermatol.2010.317

[30] Uitto J, Christiano AM. Molecular basis for the dystrophic forms of epidermolysis bullosa: Mutations in the type VII collagen gene. Archives of Dermatological Research. 1994;**287**(1):16-22 7963683

[31] Chung HJ, Uitto J. Type VII collagen: The anchoring fibril protein at fault in dystrophic epidermolysis bullosa. Dermatologic Clinics. 2010 Jan;**28**(1):93-105. DOI: 10.1016/j.det.2009.10.011

[32] Christiano AM, Greenspan DS, Lee S, et al. Cloning of human type VII collagen. Complete primary sequence of the alpha 1(VII) chain and identification of intragenic polymorphisms. The Journal of Biological Chemistry 1994 Aug 12;**269**(32):20256-20262. PMID: 8051117

[33] Jones DA, Hunt SW 3rd, Prisayanh PS, et al. Immunodominant autoepitopes of type VII collagen are short, paired peptide sequences within the fibronectin type III homology region of the noncollagenous (NC1) domain. The Journal of Investigative Dermatology 1995 Feb;**104**(2):231-235. DOI: 10.1111/1523-1747.ep12612780

[34] Gammon WR, Abernethy ML, Padilla KM, et al. Noncollagenous (NC1) domain of collagen VII resembles multidomain adhesion proteins involved in tissue-specific organization of extracellular matrix. The Journal of Investigative Dermatology. 1992 Dec;**99**(6):691-696. DOI: 10.1111/1523-1747.ep12614080

[35] Kim JH, Kim SC. Epidermolysis bullosa acquisita. Journal of the European Academy of Dermatology and Venereology. 2013 Oct;**27**(10):1204-1213. DOI: 10.1007/s40257-014-0098-0

[36] Sakai LY, Keene DR, Morris NP, et al. Type VII collagen is a major structural component of anchoring fibrils. The Journal of Cell Biology. 1986 Oct;**103**(4):1577-1586. DOI: 10.1083/jcb.103.4.1577

[37] Bruckner-Tuderman L, Nilssen O, Zimmermann DR, et al. Immunohistochemical and mutation analyses demonstrate that procollagen VII is processed to collagen VII through removal of the NC-2 domain. The Journal of Cell Biology. 1995 Oct;**131**(2):551-559. DOI: 10.1083/jcb.131.2.551

[38] Chen M, Marinkovich MP, Veis A, et al. Interactions of the amino-terminal noncollagenous (NC1) domain of type VII collagen with extracellular matrix components. A potential role in epidermal-dermal adherence in human skin. The Journal of Biological Chemistry. 1997 Jun 6;**272**(23):14516-14522. DOI: 10.1074/jbc.272.23.14516

[39] Chen M, Marinkovich MP, Jones JC, et al. NC1 domain of type VII collagen binds to the beta3 chain of laminin 5 via a unique subdomain within the fibronectin-like repeats. The Journal of Investigative Dermatology. 1999 Feb;**112**(2):177-183. DOI: 10.1046/j.1523-1747.1999.00491.x

[40] Villone D, Fritsch A, Koch M, et al. Supramolecular interactions in the dermo-epidermal junction zone: Anchoring fibril-collagen VII tightly binds to banded collagen fibrils. The Journal of Biological Chemistry. 2008 Sep 5;**283**(36):24506-24513. DOI: 10.1074/jbc.M802415200

[41] Tanaka T, Furukawa F, Imamura S. Epitope mapping for epidermolysis bullosa acquisita autoantibody by molecularly cloned cDNA for type VII collagen. The Journal of Investigative Dermatology. 1994 May;**102**(5):706-709. DOI: 10.1111/1523-1747.ep12374333

[42] Lapiere JC, Woodley DT, Parente MG, et al. Epitope mapping of type VII collagen. Identification of discrete peptide sequences recognized by sera from patients with acquired epidermolysis bullosa. The Journal of Clinical Investigation. 1993 Oct;**92**(4):1831-1839. DOI: 10.1172/JCI116774

[43] Gammon WR, Inman 3rd AO, Wheeler Jr CE. Differences in complement-dependent chemotactic activity generated by bullous pemphigoid and epidermolysis bullosa acquisita immune complexes: Demonstration by leukocytic attachment and organ culture methods. The Journal of Investigative Dermatology 1984 Jul;**83**(1):57-61. DOI: 10.1111/1523-1747.ep12261694

[44] Sitaru C, Kromminga A, Hashimoto T, et al. Autoantibodies to type VII collagen mediate Fcgamma-dependent neutrophil activation and induce dermal-epidermal separation in cryosections of human skin. The American Journal of Pathology. 2002 Jul;**161**(1):301-311. DOI: 10.1016/S0002-9440(10)64182-X

[45] Sitaru C, Mihai S, Otto C, et al. Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. Journal of Clinical Investigation. 2005 Apr;**115**(4):870-878. DOI: 10.1172/JCI200521386

[46] Sitaru C, Chiriac MT, Mihai S, et al. Induction of complement-fixing autoantibodies against type VII collagen results in subepidermal blistering in mice. Journal of Immunology. 2006 Sep 1;**177**(5):3461-3468. DOI: 10.4049/jimmunol.177.5.3461

[47] Mihai S, Chiriac MT, Takahashi K, et al. The alternative pathway of complement activation is critical for blister induction in experimental epidermolysis bullosa acquisita. Journal of Immunology. 2007 May 15;**178**(10):6514-6521. DOI: 10.4049/jimmunol.178.10.6514

[48] Chiriac MT, Roesler J, Sindrilaru A, et al. NADPH oxidase is required for neutrophil-dependent autoantibody-induced tissue damage. The Journal of Pathology. 2007 May;**212**(1):56-65. DOI: 10.1002/path.2157

[49] Chen M, Doostan A, Bandyopadhyay P, et al. The cartilage matrix protein subdomain of type VII collagen is pathogenic for epidermolysis bullosa acquisita. The American Journal of Pathology. 2007 Jun;**170**(6):2009-2018. DOI: 10.2353/ajpath.2007.061212

[50] Park SB, Cho KH, Youn JL, et al. Epidermolysis bullosa acquisita in childhood – A case mimicking chronic bullous dermatosis of childhood. Clinical and Experimental Dermatology. 1997 Sep;**22**(5):220-222. DOI: 10.1111/j.1365-2230.1997.tb01072.x

[51] Chen M, Keene DR, Costa FK, et al. The carboxyl terminus of type VII collagen mediates antiparallel dimer formation and constitutes a new antigenic epitope for epidermolysis Bullosa acquisita autoantibodies. The Journal of Biological Chemistry. 2001 Jun 15;**276**(24):21649-21655. DOI: 10.1074/jbc.M100180200

[52] Tanaka H, Ishida-Yamamoto A, Hashimoto T, et al. A novel variant of acquired epidermolysis bullosa with autoantibodies against the central triple-helical domain of type VII collagen. Laboratory Investigation. 1997 Dec;**77**(6):623-632 9426400

[53] Schmidt E, Höpfner B, Chen M, et al. Childhood epidermolysis bullosa acquisita: A novel variant with reactivity to all three structural domains of type VII collagen. The British Journal of Dermatology. 2002 Sep;**147**(3):592-597. DOI: 10.1046/j.1365-2133.2002.04863.x

[54] Ishii N, Yoshida M, Ishida-Yamamoto A, et al. Some epidermolysis bullosa acquisita sera react with epitopes within the triple-helical collagenous domain as indicated by immunoelectron microscopy. The British Journal of Dermatology. 2009 May;**160**(5):1090-1093. DOI: 10.1111/j.1365-2133.2008.08952.x

[55] Ishii N, Yoshida M, Hisamatsu Y, et al. Epidermolysis bullosa acquisita sera react with distinct epitopes on the NC1 and NC2 domains of type VII collagen: Study using immunoblotting of domain-specific recombinant proteins and postembedding immunoelectron microscopy. The British Journal of Dermatology. 2004 May;**150**(5):843-851. DOI: 10.1111/j.1365-2133.2004.05933.x

[56] Gandhi K, Chen M, Aasi S, et al. Autoantibodies to type VII collagen have heterogeneous subclass and light chain compositions and their complement-activating capacities do not correlate with the inflammatory clinical phenotype. Journal of Clinical Immunology. 2000 Nov;**20**(6):416-423. DOI: 10.1023/A:1026451530967

[57] Recke A, Sitaru C, Vidarsson G, et al. Pathogenicity of IgG subclass autoantibodies to type VII collagen: Induction of dermal-epidermal separation. Journal of Autoimmunity. 2010 Jun;**34**(4):435-444. DOI: 10.1016/j.jaut.2009.11.003

[58] Cho HJ, Lee IJ, Kim SC. Complement-fixing abilities and IgG subclasses of autoantibodies in epidermolysis bullosa acquisita. Yonsei Medical Journal. 1998 Aug;**39**(4):339-344. DOI: 10.3349/ymj.1998.39.4.339

[59] Kasperkiewicz M, Nimmerjahn F, Wende S, et al. Genetic identification and functional validation of FcγRIV as key molecule in autoantibody-induced tissue injury. The Journal of Pathology. 2012a Sep;**228**(1):8-19. DOI: 10.1002/path.4023

[60] Sitaru AG, Sesarman A, Mihai S, et al. T cells are required for the production of blister-inducing autoantibodies in experimental epidermolysis bullosa acquisita. Journal of Immunology. 2010 Feb 1;**184**(3):1596-1603. DOI: 10.4049/jimmunol.0901412

[61] Shimanovich I, Mihai S, Oostingh GJ, et al. Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquisita and bullous pemphigoid. The Journal of Pathology. 2004 Dec;**204**(5):519-527. DOI: 10.1002/path.1674

[62] Ishii N, Hamada T, Dainichi T, et al. Epidermolysis bullosa acquisita: what's new? The Journal of Dermatology. 2010;**37**(3):220-230. DOI: 10.1111/j.1346-8138.2009.00799.x

[63] Vorobyev A, Ludwig RJ, Schmidt E. Clinical features and diagnosis of epidermolysis bullosa acquisita. Expert Review of Clinical Immunology. 2017 Feb;**13**(2):157-169. DOI: 10.1080/1744666X.2016.1221343

[64] Vodegel RM, de Jong MC, Pas HH, et al. IgA-mediated epidermolysis bullosa acquisita: Two cases and review of the literature. Journal of the American Academy of Dermatology 2002 Dec;**47**(6):919-925. DOI: 10.1067/mjd.2002.125079

[65] Buijsrogge JJ, Diercks GF, Pas HH, et al. The many faces of epidermolysis bullosa acquisita after serration pattern analysis by direct immunofluorescence microscopy. The British Journal of Dermatology. 2011 Jul;**165**(1):92-98. DOI: 10.1111/j.1365-2133.2011.10346.x

[66] Woodley DT, Remington J, Chen M. Autoimmunity to type VII collagen: Epidermolysis bullosa acquisita. Clinical Reviews in Allergy & Immunology. 2007 Oct;**33**(1-2):78-84. DOI: 10.1007/s12016-007-0027-6

[67] Gammon WR, Briggaman RA, Woodley DT, et al. Epidermolysis bullosa acquisita-a pemphigoid-like disease. Journal of the American Academy of Dermatology. 1984 Nov;**11**(5Pt 1):820-832. DOI: 10.1016/S0190-9622(84)80459-4

[68] Dahl MG. Epidermolysis bullosa acquisita-a sign of cicatricial pemphigoid? The British Journal of Dermatology. 1979 Oct;**101**(4):475-484. DOI: 10.1111/j.1365-2133.1979.tb00030.x

[69] Stewart MI, Woodley DT, Briggaman RA. Epidermolysis bullosa acquisita and associated symptomatic esophageal webs. Archives of Dermatology. 1991 Mar;**127**(3):373-377. DOI: 10.1001/archderm.1991.01680030093013

[70] Harman KE, Whittam LR, Wakelin SH, et al. Severe, refractory epidermolysis bullosa acquisita complicated by an oesophageal stricture responding to intravenous immune globulin. The British Journal of Dermatology. 1998 Dec;**139**(6):1126-1127. DOI: 10.1046/j.1365-2133.1998.2576m.x

[71] Caux F. Diagnosis and clinical features of epidermolysis bullosa acquisita. Dermatologic Clinics. 2011 Jul;**29**(3):485-491. DOI: 10.1016/j.det.2011.03.017

[72] Wieme N, Lambert J, Moerman M, et al. Epidermolysis bullosa acquisita with combined features of bullous pemphigoid and cicatricial pemphigoid. Dermatology. 1999;**198**(3):310-313. DOI: 10.1159/000018139

[73] Asfour L, Chong H, Mee J, et al. Epidermolysis bullosa acquisita (Brunsting-Perry pemphigoid variant) localized to the face and diagnosed with antigen identification using skin deficient in type VII collagen. The American Journal of Dermatopathology. 2017 Jul;**39**(7):e90-e96. DOI: 10.1097/DAD.0000000000000829

[74] Kurzhals G, Stolz W, Meurer M, et al. Acquired epidermolysis bullosa with the clinical feature of Brunsting-Perry cicatricial bullous pemphigoid. Archives of Dermatology. 1991 Mar;**127**(3):391-395. DOI: 10.1001/archderm.1991.01680030111016

[75] Choi GS, Lee ES, Kim SC, et al. Epidermolysis bullosa acquisita localized to the face. The Journal of Dermatology. 1998 Jan;**25**(1):19-22. DOI: 10.1111/j.1346-8138.1998.tb02339.x

[76] Lazić-Mosler E, Jukić IL, Murat-Sušić S, et al. Inflammatory epidermolysis bullosa acquisita in a 4-year-old girl. Journal of Dermatology. 2015 Nov;**42**(11):1098-1100. DOI: 10.1111/1346-8138.12958

[77] Callot-Mellot C, Bodemer C, Caux F, et al. Epidermolysis bullosa acquisita in childhood. Archives of Dermatology. 1997 Sep;**133**(9):1122-1126. DOI: 10.1001/archderm.1997.03890450070008

[78] Mayuzumi M, Akiyama M, Nishie W, et al. Childhood epidermolysis bullosa acquisita with autoantibodies against the noncollagenous 1 and 2 domains of type VII collagen: Case report and review of the literature. The British Journal of Dermatology. 2006;**155**:1048-1052. DOI: 10.1111/j.1365-2133.2006.07443.x

[79] Vodegel RM, Jonkman MF, Pas HH, et al. U-serrated immunodeposition pattern differentiates type VII collagen targeting bullous diseases from other subepidermal bullous autoimmune diseases. The British Journal of Dermatology. 2004 Jul;**151**(1):112-118. DOI: 10.1111/j.1365-2133.2004.06006.x

[80] Woodley DT, Gammon WR, Briggaman RA. Epidermolysis bullosa acquisita. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB, editors. Fitzpatrick's Dermatology in General Medicine. 4th ed. New York: McGraw-Hill, 1999. pp. 702-709.

[81] Richter BJ, McNutt NS. The spectrum of epidermolysis bullosa acquisita. Archives of Dermatology. 1979 Nov;**115**(11):1325-1328. DOI: 10.1001/archderm.1979.04010110031020

[82] Gibbs RB, Minus HR. Epidermolysis bullosa acquisita with electron microscopical studies. Archives of Dermatology. 1975;**111**(2):215-220. DOI: 10.1001/archderm.1975.01630140073008

[83] Fine JD, Tyring S, Gammon WR. The presence of intra-lamina lucida blister formation in epidermolysis bullosa acquisita: Possible role of leukocytes. The Journal of Investigative Dermatology. 1989 Jan;**92**(1):27-32. DOI: 10.1111/1523-1747.ep13070463

[84] Klein GF, Hintner H, Schuler G, et al. Junctional blisters in acquired bullous disorders of the dermal-epidermal junction zone: Role of the lamina lucida as the mechanical locus minoris resistentiae. The British Journal of Dermatology. 1983 Nov;**109**(5):499-508. DOI: 10.1111/j.1365-2133.1983.tb07671.x

[85] Mehren CR, Gniadecki R. Epidermolysis bullosa acquisita: Current diagnosis and therapy. Dermatol Reports. 2011 Nov 28;**3**(3):e38. DOI: 10.4081/dr.2011.e38

[86] Bauer JW, Schaeppi H, Metze D, et al. Ocular involvement in IgA-epidermolysis bullosa acquisita. The British Journal of Dermatology. 1999;**141**:887-892. DOI: 10.1046/j.1365-2133.1999.03163.x

[87] De A, Rao R, Balachandran C. Salt split technique: A useful tool in the diagnosis of subepidermal bullous disorders. Indian Journal of Dermatology. 2010 Oct;**55**(4):334-336. DOI: 10.4103/0019-5154.74534

[88] Gammon WR, Briggaman RA, Inman AO 3rd, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. The Journal of Investigative Dermatology 1984c;**82**(2):139-144. DOI: 10.1111/1523-1747.ep12259692

[89] Pohla-Gubo G, Hintner H. Direct and indirect immunofluorescence for the diagnosis of bullous autoimmune diseases. Dermatologic Clinics. 2011 Jul;**29**:365-372. DOI: 10.1016/j.det.2011.03.001

[90] Goletz S, Hashimoto T, Zillikens D, et al. Anti-p200 pemphigoid. Journal of the American Academy of Dermatology. 2014 Jul;**71**:185-191. DOI: 10.1016/j.jaad.2014.02.036

[91] Bagan J, Lo Muzio L, Scully C. Mucosal disease series. Number III. Mucous membrane pemphigoid. Oral Diseases. 2005;**11**(4):197-218. DOI: 10.1111/j.1601-0825.2005.01140.x

[92] Chan LS, Fine JD, Briggaman RA, et al. Identification and partial characterization of a novel 105-kDalton lower lamina lucida autoantigen associated with a novel immune-mediated subepidermal blistering disease. The Journal of Investigative Dermatology. 1993 Sep;**101**(3):262-267. DOI: 10.1111/1523-1747.ep12365189

[93] Terra JB, Meijer JM, Jonkman MF, et al. The n- vs. u-serration is a learnable criterion to differentiate pemphigoid from epidermolysis bullosa acquisita in direct immunofluorescence serration pattern analysis. The British Journal of Dermatology. 2013 Jul;**169**:100-105. DOI: 10.1111/bjd.12308

[94] Kasperkiewicz M, Zillikens D, Schmidt E. Pemphigoid diseases: Pathogenesis, diagnosis, and treatment. Autoimmunity. 2012;**45**(1):55-70. DOI: 10.3109/08916934.2011.606447

[95] Terra JB, Pas HH, Hertl M, et al. Immunofluorescence serration pattern analysis as a diagnostic criterion in antilaminin-332 mucous membrane pemphigoid: Immunopathological findings and clinical experience in 10 Dutch patients. The British Journal of Dermatology. 2011;**165**:815-822. DOI: 10.1111/j.1365-2133.2011.10474.x

[96] Diercks GF, Pas HH, Jonkman MF. Immunofluorescence of autoimmune bullous diseases. Surgical Pathology Clinics. 2017;**10**:505-512. DOI: 10.1016/j.path.2017.01.011

[97] Domloge-Hultsch N, Anhalt GJ, Gammon WR, et al. Antiepiligrin cicatricial pemphigoid. A subepithelial bullous disorder. Archives of Dermatology. 1994;**130**:1521-1529. DOI: 10.1001/archderm.1994.01690120057008

[98] Chen M, Chan LS, Cai X, et al. Development of an ELISA for rapid detection of anti-type VII collagen autoantibodies in epidermolysis bullosa acquisita. The Journal of Investigative Dermatology. 1997 Jan;**108**(1):68-72. DOI: 10.1111/1523-1747.ep12285634

[99] Komorowski L, Müller R, Vorobyev A, et al. Sensitive and specific assays for routine serological diagnosis of epidermolysis bullosa acquisita. Journal of the American Academy of Dermatology. 2013 Mar;**68**(3):e89-e95. DOI: 10.1016/j.jaad.2011.12.032

[100] Saleh MA, Ishii K, Kim YJ, et al. Development of NC1 and NC2 domains of type VII collagen ELISA for the diagnosis and analysis of the time course of epidermolysis bullosa acquisita patients. Journal of Dermatological Science. 2011 Jun;**62**(3):169-175. DOI: 10.1016/j.jdermsci.2011.03.003

[101] Marzano AV, Cozzani E, Fanoni D, et al. Diagnosis and disease severity assessment of epidermolysis bullosa acquisita by ELISA for anti-type VII collagen autoantibodies: An Italian multicentre study. The British Journal of Dermatology. 2013 Jan;**168**(1):80-84. DOI: 10.1111/bjd.12011

[102] De Jong MC, Bruins S, Heeres K, et al. Bullous pemphigoid and epidermolysis bullosa acquisita. Differentiation by fluorescence overlay antigen mapping. Archives of Dermatology. 1996 Feb;**132**(2):151-157. DOI: 10.1001/archderm.1996.03890260053008

[103] Reddy H, Shipman AR, Wojnarowska F. Epidermolysis bullosa acquisita and inflammatory bowel disease: A review of the literature. Clinical and Experimental Dermatology. 2013;**38**(3):225-229. DOI: 10.1111/ced.12114

[104] Chen M, O'Toole EA, Sanghavi J, et al. The epidermolysis bullosa acquisita antigen (type VII collagen) is present in human colon and patients with crohn's disease have autoantibodies to type VII collagen. The Journal of Investigative Dermatology. 2002 Jun;**118**(6):1059-1064. DOI: 10.1046/j.1523-1747.2002.01772.x

[105] Schulze F, Neumann K, Recke A, et al. Malignancies in pemphigus and pemphigoid diseases. The Journal of Investigative Dermatology. 2015;**135**(5):1445-1447. DOI: 10.1038/jid.2014.547

[106] Hoshina D, Sawamura D, Nomura T, et al. Epidermolysis bullosa acquisita associated with psoriasis vulgaris. Clinical and Experimental Dermatology. 2007 Sep;**32**(5):516-518. DOI: 10.1111/j.1365-2230.2007.02430.x

[107] Krivo JM, Miller F. Immunopathology of epidermolysis bullosa acquisita. Association with mixed cryoglobulinemia. Archives of Dermatology. 1978 Aug;**114**(8):1218-1220. DOI: 10.1001/archderm.1978.01640200072019

[108] Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita-successful treatment with colchicine. Archives of Dermatological Research. 1994;**286**(1):35-46. DOI: 10.1007/BF00375841

[109] Gürcan HM, Ahmed AR. Current concepts in the treatment of epidermolysis bullosa acquisita. Expert Opinion on Pharmacotherapy. 2011 Jun;**12**(8):1259-1268. DOI: 10.1517/14656566.2011.549127

[110] Crow LL, Finkle JP, Gammon WR, et al. Clearing of epidermolysis bullosa acquisita with cyclosporine. Journal of the American Academy of Dermatology. 1988 Nov;**19**(5 Pt 2):937-942. DOI: 10.1016/S0190-9622(88)70254-6

[111] Kofler H, Wambacher-Gasser B, Topar G, et al. Intravenous immunoglobulin treatment in therapy-resistant epidermolysis bullosa acquisita. Journal of the American Academy of Dermatology. 1997 Feb;**36**(2 Pt 2):331-335. DOI: 10.1016/S0190-9622(97)80411-2

[112] Sadler E, Schafleitner B, Lanschuetzer C, et al. Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. The British Journal of Dermatology. 2007 Aug;**157**(2):417-419. DOI: 10.1111/j.1365-2133.2007.08048.x

[113] Le Roux-Villet C, Prost-Squarcioni C. Epidermolysis bullosa acquisita: Literature review. Annales de Dermatologie et de Vénéréologie 2011 Mar;**138**(3):228-246. DOI: 10.1016/j.annder.2011.01.019

[114] Fortuna G, Marinkovich MP. Linear immunoglobulin A bullous dermatosis. Clinics in Dermatology. 2012;**30**:38-50. DOI: 10.1016/j.clindermatol.2011.03.008

[115] Lings K, Bygum A. IgA bullous dermatosis: A retrospective study of 23 patients in Denmark. Acta Dermato-Venereologica. 2015;**95**:466-471. DOI: 10.2340/00015555-1990

[116] Antiga E, Caproni M, Fabbri P. Linear immunoglobulin a bullous dermatosis: Need for an agreement on diagnostic criteria. Dermatology. 2013;**226**:329-332. DOI: 10.1159/000350818

[117] Horváth B, Jonkman BF. Linear IgA Disease. Autoimmune Bullous Diseases. Switzerland: Springer International Publishing; 2016. pp. 157-163. DOI: 10.1007/978-3-319-23754-1_18

[118] Ishii N. Prognostic factors of patients with linear IgA bullous dermatosis. The British Journal of Dermatology. 2017;**177**(1):16-17. DOI: 10.1111/bjd.15603

[119] Tsuchisaka A, Ohara K, Ishii N, et al. Type VII collagen is the major autoantigen for sublamina densa-type linear IgA bullous dermatosis. The Journal of Investigative Dermatology. 2015;**135**:626-629. DOI: 10.1038/jid.2014.381

[120] Sakaguchi M, Bito T, Oda Y, et al. Three cases of linear IgA/IgG bullous dermatosis showing IgA and IgG reactivity with multiple antigens, particularly laminin-332. JAMA Dermatology. 2013;**149**:1308-1313. DOI: 10.1001/jamadermatol.2013.5691

[121] Vargas TJ, Fialho M, Santos LT, Rodrigues PA, Vargas AL, Sousa MA. Linear IgA dermatosis associated with ulcerative colitis: Complete and sustained remission after total colectomy. Anais Brasileiros de Dermatologia. 2013;**88**:600-603. DOI: 10.1590/abd1806-4841.20131949

[122] Patrício P, Ferreira C, Gomes MM, Filipe P. Autoimmune bullous dermatoses: a review. Annals of the New York Academy of Sciences. 2009;**1173**:203-210. DOI: 10.1111/j.1749-6632.2009.04737.x

[123] Bowen JT. Six cases of bullous dermatitis following vaccination, and resembling dermatitis herpetiformis. Journal of Cutaneous Diseases. 1901;**19**:401-423

[124] Jordon RE, Bean SF, Triftshauser CT, et al. Childhood bullous dermatitis herpetiformis. Negative immunofluorescent tests. Archives of Dermatology. 1970;**101**:629-634. DOI: 10.1001/archderm.1970.04000060001001

[125] Chorzelski TP, Jablonska S. IgA linear dermatosis of childhood (chronic bullous disease of childhood). The British Journal of Dermatology. 1979;**101**:535-542. DOI: 10.1111/j.1365-2133.1979.tb15096.x

[126] Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Bröcker E.Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. Archives of Dermatology. 1995;**131**:957-958. DOI: 10.1001/archderm.1995.01690200097021

[127] Nanda A, Dvorak R, Al-Sabah H, Alsaleh QA. Linear IgA bullous disease of childhood: An experience from Kuwait. Pediatric Dermatology. 2006;**23**:443-447. DOI: 10.1111/j.1525-1470.2006.00279.x

[128] Mulyowa GK, Jaeger G, Kabakyenga J, Bröcker EB, Zillikens D, Schmidt E. Autoimmune subepidermal blistering diseases in Uganda: Correlation of autoantibody class with age of patients. International Journal of Dermatology. 2006;**45**:1047-1052. DOI: 10.1111/j.1365-4632.2006.02750.x

[129] Aboobaker J, Wojnarowska FT, Bhogal B, Black MM. Chronic bullous dermatosis of childhood – Clinical and immunological features seen in African patients. Clinical and Experimental Dermatology. 1991;**16**:160-164. DOI: 10.1111/j.1365-2230.1991.tb00336.x

[130] Mahé A, Flageul B, Bobin P. Bullous IgA linear dermatosis of children in Mali. Annales de Dermatologie et de Vénéréologie. 1996;**123**:544-548 9615104

[131] Kenani N, Mebazaa A, Denguezli M, et al. Childhood linear IgA bullous dermatosis in Tunisia. Pediatric Dermatology. 2009;**26**:28-33. DOI: 10.1111/j.1525-1470.2008.00817.x

[132] Reid C, Wojnarowska F, Pothupityiyia G, et al. Chronic bullous dermatosis of childhood around the world. British Journal of Dermatology. 1988;**119**(33):41. DOI: 10.1111/j.1365-2133.1988.tb05375.x

[133] Wojnarowska F, Marsden RA, Bhogal B, et al. Chronic bullous disease of childhood, childhood cica-tricial pemphigoid, and linear IgA disease of adults. A comparative study demonstrating clinical and immunopathologic overlap. Journal of the American Academy of Dermatology. 1988;**19**:792-805. DOI: 10.1016/S0190-9622(88)70236-4

[134] Gluth MB, Witman PM, Thompson DM. Upper aerodigestive tract complications in a neonate with linear IgA bullous dermatosis. International Journal of Pediatric Otorhinolaryngology. 2004;**68**(7):965-970. DOI: 10.1016/j.ijporl.2004.02.014

[135] Collier PM, Wojnarowska F, Welsh K, et al. Adult linear IgA disease and chronic bullous disease of childhood: The association with human lymphocyte antigens Cw7, B8, DR3 and tumour necrosis factor influences disease expression. The British Journal of Dermatology. 1999;**141**:867. DOI: 10.1046/j.1365-2133.1999.03110.x

[136] Kanwar AJ, Sandhu K, Handa S. Chronic bullous dermatosis of childhood in North India. Pediatric Dermatology. 2004;**21**:610-612. DOI: 10.1111/j.0736-8046.2004.21521.x

[137] Nousari HC, Kimyai-Asadi A, Caeiro JP, Anhalt GJ. Clinical, demographic, and Immunohistologic features of vancomycin-induced linear IgA bullous disease of the skin report of 2 cases and review of the literature. Medicine (Baltimore). 1999;**78**(1):1-8 9990350

[138] Hull CM, Zone J, Bologna JL, Jorizzo JL, Rapini R. Dermatology. 2nd ed. Rio de Janeiro: Elsevier; 2008. Dermatosis Herpetiformis and Linear IgA bullous Dermatosis; pp. 447-457

[139] Camilleri M, Pace JL. Drug-induced linear immunoglobulin-A bullous dermatosis. Clinics in Dermatology. 1998;**16**(3):389-391. DOI: 10.1016/S0738-081X(98)00009-1

[140] Adler NR, McLean CA, Aung AK, Goh MS. Piperacillin-tazobactam-induced linear IgA bullous dermatosis presenting clinically as Stevens-Johnson syndrome/toxic epidermal necrolysis overlap. Clinical and Experimental Dermatology. 2017;**42**(3):299-302. DOI: 10.1111/ced.13030

[141] Becker JG, Mundi JP, Newlove T, Mones J, Shupack J. Development of linear IgA bullous dermatosis in a patient with psoriasis taking ustekinumab. Journal of the American Academy of Dermatology. 2012;**67**:150-151. DOI: 10.1016/j.jaad.2011.11.955

[142] Hoffmann J, Hadaschik E, Enk A, Stremmel W, Gauss A. Linear IgA bullous Dermatosis secondary to infliximab therapy in a patient with ulcerative colitis. Dermatology. 2015;**231**(2):112-115. DOI: 10.1159/000431172

[143] Palmer RA, Ogg G, Allen J, et al. Vancomycin-induced linear IgA disease with autoantibodies to BP180 and LAD285. The British Journal of Dermatology. 2001;**145**:816-820. DOI: 10.1046/j.1365-2133.2001.04492.x

[144] Barnadas MA, Moreno A, Brunet SG, et al. Linear IgA bullous dermatosis associated with Hodgkin's disease [letter]. Journal of the American Academy of Dermatology. 1988;**19**:1122-1124 3060488

[145] Godfrey K, Wojnarowska F, Leonard J. Linear IgA disease of adults: Association with lymphoproliferative malignancy and possible role of other triggering factors. The British Journal of Dermatology. 1990;**123**(4):447-452. DOI: 10.1111/j.1365-2133.1990.tb01448.x

[146] Kartan S, Shi VY, Clark AK, Chan LS. Paraneoplastic pemphigus and autoimmune blistering diseases associated with neoplasm: Characteristics, diagnosis, associated neoplasms, proposed pathogenesis, treatment. American Journal of Clinical Dermatology. 2017;**18**(1):105-126. DOI: 10.1007/s40257-016-0235-z

[147] McEvoy MT, Connolly SM. Linear IgA dermatosis: Association with malignancy. Journal of the American Academy of Dermatology. 1990;**22**:59-63. DOI: 10.1016/0190-9622(90)70008-6

[148] Ikeya S, Urano S, Tokura Y. Linear IgA bullous dermatosis following human papillomavirus vaccination. European Journal of Dermatology. 2012;**22**(6):787-788. DOI: 10.1684/ejd.2012.1851

[149] Thune P, Eeg-Larsen T, Nilsen R. Acute linear IgA dermatosis in a child following varicella. Archives of Dermatology. 1984;**120**:1237-1238. DOI: 10.1001/archderm.1984.01650450119034

[150] Blickenstaff RD, Perry HO, Peters MS. Linear IgA deposition associated with cutaneous varicella-zoster infection: A case report. Journal of Cutaneous Pathology. 1988;**15**:49-52. DOI: 10.1111/j.1600-0560.1988.tb00516.x

[151] Onoe A, Matsuura D, Terui T, et al. Linear immunoglobulin A/G bullous dermatosis associated with ulcerative colitis. J Dermatol. 2017 Nov;**44**(11):1295-1298. DOI: 10.1111/1346-8138.13934

[152] Yamaguchi Y, Ujiie H, Ohigashi H et al. Linear IgA Bullous Dermatosis Associated with Immunoglobulin light-chain amyloidosis. Acta Dermato-Venereologica. 2017 Jun;**97**(4):528-529. DOI: 10.2340/00015555-2590

[153] Kakugawa T, Tomimura S, Hayashi T, et al. Interstitial pneumonia associated with linear immunoglobulin A/immunoglobulin G bullous dermatosis. Respiration. 2013;**86**: 347-351. DOI: 10.1159/000351427

[154] Hayakawa K, Shiohara T, Yagita A, Nagashima M. Linear IgA bullous dermatosis associated with rheumatoid arthritis. Journal of the American Academy of Dermatology. 1992;**26**(1):110-113. DOI: 10.1016/0190-9622(92)70017-A

[155] Lee HJ, Yun SJ, Lee SC, Lee JB. A case of linear IgA bullous Dermatosis associated with systemic lupus Erythematosus. Annals of Dermatology. 2016;**28**(5):660-662. DOI: 10.5021/ad.2016.28.5.660

[156] Egan CL, Liu V, Harris RM, White SM, Lessin SR, Weinberg JM. Linear IgA disease associated with membranous glomerulonephropathy. International Journal of Dermatology. 2000;**39**:379-382. DOI: 10.1046/j.1365-4362.2000.00841-6.x

[157] Ohata C, Ishii N, Koga H, Nakama TA. Clinical and serological study of linear IgA bullous dermatosis without linear immunoglobulin deposition other than IgA at the basement membrane zone. The British Journal of Dermatology. 2017;**177**:152-157. DOI: 10.1111/bjd.15232

[158] Georgi M, Scheckenbach C, Kromminga A, et al. Mapping of epitopes on the BP180 ectodomain targeted by IgA and IgG autoantibodies in patients with the lamina lucida-type of linear IgA disease. Archives of Dermatological Research. 2001;**293**:109-114. DOI: 10.1007/s004030000205

[159] Willsteed E, Bhogal BS, Black MM, et al. Use of 1M NaCl split skin in the direct immunofluorescence of the linear IgA bullous dermatoses. Journal of Cutaneous Pathology. 1990;**17**:144-148. DOI: 10.1111/j.1600-0560.1990.tb00073.x

[160] Zone JJ, Taylor TB, Kadunce DP, et al. Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin a bullous dermatosis. The Journal of Clinical Investigation. 1990;**85**:812-820. DOI: 10.1172/JCI114508

[161] Marinkovich MP, Taylor TB, Keene DR, et al. LAD-1, the linear IgA bullous dermatosis autoantigen, is a novel 120-kDa anchoring filament protein synthesized by epidermal cells. The Journal of Investigative Dermatology. 1996;**106**:734-738. DOI: 10.1111/1523-1747.ep12345782

[162] Hirako Y, Usukura J, Uematsu J, et al. Cleavage of BP180, a 180-kDa bullous pemphigoid antigen, yields a 120-kDa collagenous extracellular polypeptide. The Journal of Biological Chemistry. 1998;**273**:9711-9717. DOI: 10.1074/jbc.273.16.9711

[163] Zone JJ, Taylor TB, Meyer LJ, et al. The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAg2. The Journal of Investigative Dermatology. 1998;**110**:207-210. DOI: 10.1046/j.1523-1747.1998.00129.x

[164] Allen J, Wojnarowska F. Linear IgA disease: The IgA and IgG response to the epidermal antigens demonstrates that intermolecular epitope spreading is associated with IgA rather than IgG antibodies, and is more common in adults. The British Journal of Dermatology. 2003;**149**(5):977-985. DOI: 10.1111/j.1365-2133.2003.05648.x

[165] Franzke CW, Bruckner-Tuderman L, Blobel CP. Shedding of collagen XVII/BP180 in skin depends on both ADAM10 and ADAM9. The Journal of Biological Chemistry. 2009;**284**:23386-23396. DOI: 10.1074/jbc.M109.034090

[166] Ishiko A, Shimizu H, Masunaga T, et al. 97 kDa linear IgA bullous dermatosis antigen localizes in the lamina lucida between the NC16A and carboxyl terminal domains of the 180 kDa bullous pemphigoid antigen. The Journal of Investigative Dermatology. 1998;**111**:93-96. DOI: 10.1046/j.1523-1747.1998.00231.x

[167] Zillikens D, Herzele K, Georgi M, et al. Autoantibodies in a subgroup of patients with linear IgA disease react with the NC16A domain of BP1801. The Journal of Investigative Dermatology. 1999;**113**:947-953. DOI: 10.1046/j.1523-1747.1999.00808.x

[168] SC1 H, Voith U, Schönau V, et al. Plasmin plays a role in the in vitro generation of the linear IgA dermatosis antigen LADB97. The Journal of Investigative Dermatology. 2009;**129**(7):1730-1739. DOI: 10.1038/jid.2008.424

[169] Hirako Y, Nishizawa Y, Sitaru C, et al. The 97-kDa (LABD97) and 120-kDa (LAD-1) fragments of bullous pemphigoid antigen 180/type XVII collagen have different N-termini. The Journal of Investigative Dermatology. 2003;**121**(6):1554. DOI: 10.1046/j.1523-1747.2003.12607.x

[170] Dmochowski M, Hashimoto T, Bhogal BS, et al. Immunoblotting studies of linear IgA disease. Journal of Dermatological Science. 1993;**6**:194-200. DOI: 10.1016/0923-1811(93)90038-Q

[171] Zambruno G, Manca V, Kanitakis J, et al. Linear IgA bullous dermatosis with autoantibodies to a 290 kd antigen of anchoring fibrils. Journal of the American Academy of Dermatology. 1994;**31**:884-888. DOI: 10.1016/S0190-9622(94)70252-7

[172] Venning VA. Linear IgA disease: Clinical presentation, diagnosis, and pathogenesis. Immunology and Allergy Clinics of North America. 2012;**32**(2):245-253. DOI: 10.1016/j.iac.2012.04.004

[173] Allen J, Wojnarowska F. Linear IgA disease: The IgA and IgG response to dermal antigens demonstrates a chiefly IgA response to LAD285 and a dermal 180-kDa protein. The British Journal of Dermatology. 2003b;**149**:1055-1058. DOI: 10.1111/j.1365-2133.2003.05648.x

[174] Gottlieb J, Ingen-Housz-Oro S, Alexandre M, et al. Idiopathic linear IgA bullous dermatosis: Prognostic factors based on a case series of 72 adults. The British Journal of Dermatology. 2017;**177**:212-222. DOI: 10.1111/bjd.15244

[175] Ghohestani RF, Nicolas JF, Kanitakis J, Claudy A. Linear IgA bullous dermatosis with IgA antibodies exclusively directed against the 180- or 230-kDa epidermal antigens. The Journal of Investigative Dermatology. 1997;**108**:854-858. DOI: 10.1111/1523-1747.ep12292581

[176] Li X, Tsuchisaka A, Qian H, et al. Linear IgA/IgG bullous dermatosis reacts with multiple laminins and integrins. European Journal of Dermatology. 2015;**25**:418-423. DOI: 10.1684/ejd.2015.2555

[177] Egan CA, Martineau MR, Taylor TB, et al. IgA antibodies recognizing LABD97 are predominantly IgA1 subclass. Acta Dermato-Venereologica. 1999a;**79**:343-346 10494707

[178] Caproni M, Rolfo S, Bernacchi E, Bianchi B, Brazzini B, Fabbri P. The role of lymphocytes, granulocytes, mast cells and their related cy- tokines in lesional skin of linear IgA bullous dermatosis. The British Journal of Dermatology. 1999;**140**:1072-1078. DOI: 10.1046/j.1365-2133.1999.02904.x

[179] Bouldin MB, Clowers-Webb HE, Davis JL, et al. Naproxen-associated linear IgA bullous dermatosis: Case report and review. Mayo Clinic Proceedings. 2000;**75**:967-970. DOI: 10.4065/75.9.967

[180] Zone JJ, Egan CA, Taylor TB, et al. IgA autoimmune disorders: Development of a passive transfer mouse model. The Journal of Investigative Dermatology. Symposium Proceedings. 2004;**9**:47-51. DOI: 10.1111/j.1087-0024.2004.00840.x

[181] Rao CR, Hall RP: Linear IgA dermatosis and chronic bullous disease of childhood; In Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. pp. 623-629

[182] Jablonska S, Chorzelski TP, Rosinska D, et al. Linear IgA bullous dermatosis of childhood (chronic bullous dermatosis of childhood). Clinics in Dermatology. 1991;**9**:393-401. DOI: 10.1016/0738-081X(91)90031-F

[183] Torchia D, Caproni M, Del Bianco E, et al. Linear IgA disease presenting as prurigo nodularis. The British Journal of Dermatology. 2006;**155**:479-480. DOI: 10.1111/j.1365-2133.2006.07315.x

[184] Yoneda K, Yokoi I, Demitsu T, et al. Localized linear IgA disease showing contact dermatitis-like eruption. European Journal of Dermatology. 2007;**17**:339-340. DOI: 10.1684/ejd.2007.0215

[185] Chorzelski TP, Jabłońska S, Maciejowska E. Linear IgA bullous dermatosis of adults. Clinics in Dermatology. 1991;**9**(3):383-392. DOI: 10.1016/0738-081X(91)90030-O

[186] Kelly SE, Frith PA, Millard PR, et al. A clinicopathological study of mucosal involvement in linear IgA disease. The British Journal of Dermatology. 1988;**119**:161-170. DOI: 10.1111/j.1365-2133.1988.tb03197.x

[187] Cohen DM, Bhattacharyya I, Zunt SL, Tomich CE. Linear IgA disease histopathologically and clinically masquerading as lichen planus. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 1999;**88**:196-201. DOI: 10.1016/S1079-2104(99)70117-4

[188] Porter SR, Bain SE, Scully CM. Linear IgA disease manifesting as recalcitrant desquamative gingivitis. Oral Surgery, Oral Medicine, and Oral Pathology. 1992;**74**(2):179-182. DOI: 10.1016/0030-4220(92)90379-5

[189] Letko E, Bhol K, Foster CS, et al. Linear IgA bullous disease limited to the eye: A diagnostic dilemma: Response to intravenous immunoglobulin therapy. Ophthalmology. 2000;**107**(8):1524. DOI: 10.1016/S0161-6420(00)00245-1

[190] Chanal J, Ingen-Housz-Oro S, Ortonne N, et al. Linear IgA bullous dermatosis: Comparison between the druginduced and spontaneous forms. The British Journal of Dermatology. 2013;**169**:1041-1048. DOI: 10.1111/bjd.12488

[191] Kuechle MK, Stegemeir E, Maynard B, et al. Druginduced linear IgA bullous dermatosis: Report of six cases and review of the literature. Journal of the American Academy of Dermatology. 1994;**30**:187-192. DOI: 10.1016/S0190-9622(94)70015-X

[192] A1 P-B, Sánchez-Sambucety P, Rodríguez-Prieto MÁ. A morbilliform variant of linear IgA dermatosis: A new case. International Journal of Dermatology. 2011;**50**(12):1528-1530. DOI: 10.1111/j.1365-4632.2011.05099.x

[193] Walsh SN, Kerchner K, Sanguexa OP. Localized palmar vancomycin-induced linear IgA bullous dermatosis occuring at supratherapeutic levels. Archives of Dermatology. 2009;**145**(5):603-604. DOI: 10.1001/archdermatol.2009.68

[194] Curtis JA, Zone JJ. Linear IgA bullous Dermatosis. In: Autoimmune Bullous Diseases. Switzerland: Springer International Publishing; 2016. pp. 117-132. DOI: 10.1007/978-3-319-26728-9_7

[195] Smith SB, Harrist TJ, Murphy GF, et al. Linear IgA bullous dermatosis v dermatitis herpetiformis. Quantitative measurements of dermoepidermal alterations. Archives of Dermatology. 1984;**120**(3):324-328. DOI: 10.1001/archderm.1984.01650390046009

[196] Guide SV, Marinkovich MP. Linear IgA bullous dermatosis. Clinics in Dermatology. 2001;**19**:719-727. DOI: 10.1016/S0738-081X(00)00185-1

[197] Collier PM, Wojnarowska F, Millard PR. Variation in the deposition of the antibodies at different anatomical sites in linear IgA disease of adults and chronic bullous disease of childhood. The British Journal of Dermatology. 1992;**127**(5):482-484. DOI: 10.1111/j.1365-2133.1992.tb14844.x

[198] Van L, Browning JC, Krishnan RS, et al. Dermatitis herpetiformis: Potential for confusion with linear IgA bullous dermatosis on direct immunofluorescence. Dermatology Online Journal 2008;**14**:21. PMID: 18319038

[199] Ramirez-Quizon MN, Murrell DF. Linear IgA Disease. Blistering Diseases. Berlin Heidelberg: Springer; 2015. pp. 351-356. DOI: 10.1007/978-3-662-45698-9_33

[200] Klein PA, Callen JP. Linear IgA Dermatosis. 2010 Sep 28. Available from: http://emedicine.medscape.com/article/1063590-overview [Accessed: Apr 20, 2011]

[201] Gammon WR, Briggaman RA, Inman AO III, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. The Journal of Investigative Dermatology. 1984;**82**:139-144. DOI: 10.1111/1523-1747.ep12259692

[202] Lally A, Chamberlain A, Allen J, et al. Dermal-binding linear IgA disease: An uncommon subset of a rare immunobullous disease. Clinical and Experimental Dermatology. 2007;**32**:493-498. DOI: 10.1111/j.1365-2230.2007.02428.x

[203] Wojnarowska F, Collier PM, Allen J, Millard PR. The localization of the target antigens and antibodies in linear IgA disease is heterogeneous, and dependent on the methods used. The British Journal of Dermatology. 1995;**132**(5):750-757. DOI: 10.1111/j.1365-2133.1995.tb00721.x

[204] Zhou S, Ferguson DJ, Allen J, Wojnarowska F. The localization of target antigens and autoantibodies in linear IgA disease is variable: Correlation of immuno- gold electron microscopy and immunoblotting. The British Journal of Dermatology. 1998;**139**(4): 591-597. DOI: 10.1046/j.1365-2133.1998.02453.x

[205] Karpouzis A, Vamvassakis E, Stavrianeas N, Koumantaki-Mathioudaki E, Karpouzi M, Vareltzides A. Ultrastructural immunocytochemistry of autoimmune bullous diseases. The Australasian Journal of Dermatology. 2002;**43**(2):113-119. DOI: 10.1046/j.1440-0960.2002.00571.x

[206] Mihályi L, Kiss M, Dobozy A, Kemény L, Husz S. Clinical relevance of autoantibodies in patients with autoimmune bullous dermatosis. Clinical & Developmental Immunology. 2012;**2012**:369546. DOI: 10.1155/2012/369546

[207] Sami N. Approach to the patient with autoimmune mucocutaneous blistering diseases. Dermatologic Therapy. 2011;**24**(2):173-186. DOI: 10.1111/j.1529-8019.2011.01393.x

[208] Osawa M, Demitsu T, Toda S, et al. A case of mixed bullous disease of epidermolysis bullosa acquisita and linear IgA bullous dermatosis. Dermatology. 2005;**211**(2):146-148. DOI: 10.1159/000086445

[209] Chan LS, Razzaque Ahmed A, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid. Definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic factors. Archives of Dermatology. 2002;**138**:370-379. DOI: 10.1001/archderm.138.3.370

[210] Amber KT, Murrell DF, Schmidt E, Joly P, Borradori L. Autoimmune subepidermal bullous diseases of the skin and mucosae: Clinical features, diagnosis, and management. Clin Rev Allergy Immunol. 2017 Aug;**4**. DOI: 10.1007/s12016-017-8633-4

[211] Sheridan AT, Kirtschig G, Wojnarowska F. Mixed immunobullous disease: Is this linear IgA disease? The Australasian Journal of Dermatology. 2000;**41**:219-221. DOI: 10.1046/j.1440-0960.2000.00440.x

[212] Kirtschig G, Wojnarowska F. IgA basement membrane zone autoantibodies in bullous pemphigoid detect epidermal antigens of 270-280, 230, and 180 kDa molecular weight by immunoblotting. Clinical and Experimental Dermatology. 1999;**24**:302-307. DOI: 10.1046/j.1365-2230.1999.00485.x

[213] Egan CA, Taylor TB, Meyer LJ, Petersen MJ, Zone JJ. The immunoglobulin a antibody response in clinical subsets of mucous membrane pemphigoid. Dermatology. 1999;**198**:330-335. DOI: 10.1159/000018170

[214] Letko E, Bhol K, Anzaar F, Perez VL, Ahmed AR, Foster CS. Chronic cicatrizing conjunctivitis in a patient with epidermolysis bullosa acquisita. Archives of Ophthalmology. 2006;**124**:1615-1618. DOI: 10.1001/archopht.124.11.1615

[215] Horiguchi Y, Ikoma A, Sakai R, Masatsugu A, Ohta M, Hashimoto T. Linear IgA dermatosis: Report of an infantile case and analysis of 213 cases in Japan. The Journal of Dermatology. 2008;**35**(11):737-743. DOI: 10.1111/j.1346-8138.2008.00561.x

[216] Mervic L, Dragos V, Pavlovic MD. Linear IgA bullous dermatosis of childhood: Successful treatment with miocamycin and topical corticosteroid. Clinical and Experimental Dermatology. 2009;**34**:391-392. DOI: 10.1111/j.1365-2230.2009.03366.x

[217] Lozinski A, Baum S, Sagi L, Volkov A, Trau H, Barzilai A. Rituximab (Mabthera) for treatment of rare autoimmune bullous skin disorders. Harefuah. 2012;**151**(10):562-565 23316661

[218] Legendre L, Maza A, Almalki A, Bulai-Livideanu C, Paul C, Mazereeuw-Hautier J. Botulinum toxin a: An effective treatment for linear immunoglobulin a bullous dermatosis located in the axillae. Acta Dermato-Venereologica. 2016 Jan;**96**(1):122-123. DOI: 10.2340/00015555-2178

[219] Kharfi M, Khaled A, Karaa A, Zaraa I, Fazaa B, Kamoun MR. Linear IgA bullous dermatosis: The more frequent bullous dermatosis of children. Dermatology Online Journal. 2010;**15-16**(1):2. PMID: 20137744

Chapter 5

Dermatitis Herpetiformis

Salih Levent Cinar, Demet Kartal and Murat Borlu

Additional information is available at the end of the chapter

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Abstract

Dermatitis herpetiformis is an autoimmune skin disease, which is strongly related to coeliac disease. Moreover, some authors accept it as the skin manifestation of coeliac disease. It is a chronic, recurrent disease with polymorphic skin eruptions and pruritus. Dermatitis herpetiformis is a disease of the young adults mostly, but can be seen at any age. It is characterized by papules, vesicles, excoriations, and urticarial plaques clinically. Histopathological examination reveals subepidermal separation, and with this finding, it needs to be differentiated from linear IgA bullous dermatitis and bullous pemphigoid. In this case, direct immunofluorescence is helpful. Granular deposition of IgA is pathognomonic for dermatitis herpetiformis. Dermatitis herpetiformis can accompany other autoimmune disorders such as type I diabetes mellitus, thyroid diseases, vitiligo, and collagen tissue diseases. Dermatitis herpetiformis is, usually, successfully treated with dapsone and gluten-free diet.

Keywords: autoimmune, dapsone, gluten, immunofluorescence, polymorphic eruption

1. Introduction

Autoimmune bullous diseases constitute one of the main groups of dermatological diseases. One of these bullous disorders is dermatitis herpetiformis (DH). Dermatitis herpetiformis is a chronic, recurring, autoimmune, inflammatory skin disease, which is characterized by pruritic polymorphic lesions [1].

DH was first coined by the dermatologist, Louis Duhring, in 1884. Later, in 1888, Brocq identified a similar skin disease "polymorphic pruritic dermatitis." That is why, the disease is also named as Duhring-Brocq's disease or mostly Duhring's disease [2].

DH and celiac disease (CD) are two entities that are strongly related. Moreover, there are evidences that claim that DH is the cutaneous manifestation of CD, because both diseases are

seen in gluten-sensitive persons and share similar HLA haplotypes such as DQ2 and DQ8 [3]. Today, we know that gastrointestinal symptoms in DH are generally mild or absent. We also know that only 24% of the CD patients have skin lesions resembling DH [4]. Based on these, we can consider these two diseases as different entities that are closely related.

DH is mostly reported in Caucasians although it is being increasingly reported in the Japanese population [5, 6]. Its incidence is reported to be 11.5–75.3/100,000 in different countries [7, 8]. The disease is rare in the Far East and even rarer in Afro-Americans [9]. DH mostly affects individuals in the third or fourth decades, but patients of any age between 2 and 90 have been reported so far. For example, in Italy, there are many pediatric DH patients [10]. In the adult population, males are more commonly affected, whereas female-to-male ratio ranges from 2:1 to 4:1 in children [11].

2. Pathogenesis

The pathogenesis of DH is a complex process in which autoimmune factors, genetics, HLA predisposition, and environmental factors take part [12]. In a study of monozygotic twins, the concordance rate of the disease was found to be 0.91, which was higher than expected [13]. In two other studies, 10 and 19% of the DH patients had a first-degree relative with a diagnosis of DH [14, 15].

One possible gene associated with CD and DH is myosin 9B (MYO9B) on chromosome 9p13 [16, 17]. MYO9B regulates actin cytoskeleton functions, cell integrity, and gut barrier permeability. Increased permeability of the gastrointestinal barrier may allow more gluten penetration, and as a result, immunological processes start in CD and DH [18].

In DH, close relationship with some HLA loci has also been reported. Close association between DH and HLA-DQ2/HLA-DQ8 has been emphasized. In a study of 50 patients, 86% had HLA-DQ2 allele and the rest HLA-DQ8 allele [19].

Tissue transglutaminase (tTG) is a cytoplasmic, calcium-dependent enzyme and is the major autoantigen for CD [20]. It stabilizes the cytoskeleton and the extracellular matrix by protein polymerization. As a result, it regulates the cell matrix adhesion, cell migration, and proliferation [21, 22]. tTG is also found in the skin, dermal capillaries, and basal keratinocytes [23]. tTG acts on the alcohol-soluble part of gluten, which is the gliadin, and transforms it to an autoantigen, which has an affinity for HLA-DQ2 on antigen-presenting cells. As a result, T cells are stimulated and an inflammatory cascade starts [21, 24, 25]. In addition, tTG-gliadin complexes are formed and these complexes generate a robust autoantibody response [21, 24, 25]. This continuous inflammation causes villous atrophy and intestinal damage.

The autoantibodies in DH and CD are mostly of IgA type. Sometimes, IgG can also be seen and is important in IgA deficiency [26]. The characteristic finding of DH is the deposition of IgA in the tips of dermal papillae and along the basal membrane in a granular manner. This accumulation can be seen on direct immunofluorescence of the perilesional skin [27–29]. The IgA deposits trigger an inflammatory reaction, which results in neutrophilic deposition and vesicle formation [30].

In DH, epidermal transglutaminase (eTG) seems to be the main autoantigen rather than tTG. eTG colocalizes with IgA [27–30]. The role of eTG in the skin is the cross-linking and the maintenance of cornified envelope integrity [31, 32]. eTG is expressed in dermis, small intestine, brain, and testes. Individuals with DH have IgA antibodies specific for eTG and sometimes for tTG [29]. Blood levels of IgA-type anti-eTG antibodies are more sensitive than IgA-type anti-tTG antibodies, identifying DH [33, 34]. One recent study showed that only half of the DH patients were positive for IgA anti-eTG, claiming that other possible factors take part in the pathogenesis of the disease [27]. It was shown that skin deposits of IgA immune complexes disappear with gluten-free diet (GFD) and reappear with rechallenge supporting the effect of gluten in the pathogenesis of DH [35].

Lifestyle was also shown to affect the disease activity. For example, iodine use or iodine-rich foods (such as shellfish) cause flare of DH [36]. Triiodomethane that is used during dental procedures may also cause exacerbation of the disease [37]. In two studies, it was claimed that tobacco had protective effects in CD patients similar to that observed in ulcerative colitis. But the mechanism is unclear and is not shown in DH patients [38, 39].

3. Clinical findings

DH is characterized by polymorphic lesions such as 1–3 mm papules, vesicles, small blisters, erosions, crusts, excoriations, and secondary infections [40]. Sometimes, urticarial plaques, lichenification secondary to scratching, and purpura of the fingers and toes can also be present [41, 42]. Due to scratching, representative lesions are mostly missing and all the physician sees is excoriations. In DH, the lesions are mostly seen in the extensor aspects of the body such as the anterior thigh, elbows, knees, buttocks, shoulders, sacral region, scalp, fingers, and toes. Oral mucosa is mostly spared [43]. The lesions, if not secondarily infected, heal without scar formation but with postinflammatory hyperpigmentation. In mild disease, symptomatic and disease-free periods alternate, whereas in severe disease, the symptoms are continuous with variable severity [42]. **Figure 1** demonstrates polymorphic eruption consisting of excoriated papules and erosions.

Palmoplantar purpura, which is an uncommon manifestation of DH, is mostly reported in pediatric patients. Petechiae are seen on the soles and palms sparing the dorsal surfaces. Interestingly, the dominant hands are affected more commonly suggesting that trauma can be the causative agent [44, 45]. There are also few individuals with DH, manifesting with leukocytoclastic vasculitis-like appearance, urticarial wheals, palmoplantar keratosis, and prurigo pigmentosa [46–49].

Mucosal involvement is rare in individuals with DH. Most mucosal lesions lack confirmation with direct immunofluorescence studies. These mucosal lesions are mostly thought to appear due to DH-related conditions such as CD or other autoimmune connective tissue disorders [50].

Dental abnormalities have also been reported in individuals with DH and CD. Enamel defects in permanent teeth, horizontal grooves, defects in enamel color, and enamel pits are the most commonly reported dental findings [51–53].

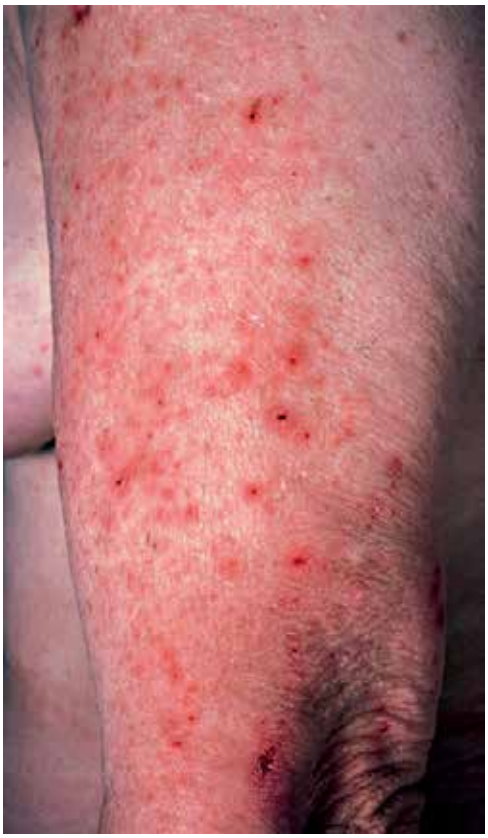

Figure 1. Excoriated papules and eroded vesicles in a patient with DH.

Only 20% of the DH patients develop gastrointestinal symptoms. These symptoms include diarrhea, anemia due to malabsorption, steatorrhea, weight loss, and malnutrition [54].

In children with DH, short stature and delayed puberty and development can be observed [55].

4. Dermatitis herpetiformis–associated disorders

DH is an autoimmune disorder and we know that different types of autoimmune disorders can coexist. Thyroid abnormalities may accompany DH. Thyroid microsomal antibodies are positive in these patients [56–58]. Thyroid involvement is mostly in the form of hypothyroidism rather than hyperthyroidism [56]. Individuals with DH have a higher risk of type I diabetes mellitus with a prevalence of 2–5% [59, 60]. Pernicious anemia, Addison's disease, vitiligo, and alopecia areata are other autoimmune diseases that are reported to coexist with DH [61–63].

Autoimmune connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome are also commonly seen in DH patients [60, 64]. **Table 1** summarizes the autoimmune disorders that may accompany DH.

• Hashimoto's thyroiditis
• Type I diabetes mellitus
• Pernicious anemia
• Addison's disease
• Alopecia areata
• Sarcoidosis
• Scleroderma
• Sjogren's disease
• Vitiligo
• Systemic lupus erythematosus
• Myasthenia gravis

Table 1. Autoimmune diseases associated with dermatitis herpetiformis.

Gjone and Nordoy, in 1970, reported for the first time that individuals with DH had a higher risk of lymphoma [65]. Some other studies also reported such relationship later on [4, 66–69]. First-degree relatives of the patients with DH are believed not to have a higher risk of lymphoma, on the contrary to CD [66, 70]. There are fewer studies asserting the contrary. Lewis et al. in 2008 reported no increased risk of morbidity or mortality in DH patients [71].

5. Diagnosis

Early diagnosis of DH is essential to relieve the patient. In consequence to understanding the pathogenesis of the disease, numerous serologic tests were developed. The proper diagnosis of DH is made with the evaluation of physical examination, immunofluorescence studies, routine histopathological examination, and the serology [3].

An ideal dermatological examination starts with inspection. Suspicious lesions, mostly excoriations, are commonly distributed on extensor aspects of the body. An intact vesicle, if visible, is the most specific diagnostic lesion. The patients mostly complain of itching that exacerbates during night, which may also be helpful in the diagnosis.

Routine histopathological examination must be performed with a specimen that contains an intact vesicle if possible [72]. Diagnostic findings are subepidermal clefts and neutrophilic infiltration at the tip of the dermal papillae. Sometimes, a few eosinophils can also be seen. These abscesses formed by neutrophils and eosinophils are called Pierard microabscess [73]. A perivascular mixed inflammation is usually present [65]. The histopathology of LABD, bullous pemphigoid, and bullous lupus erythematosus can resemble such features. Immunofluorescence studies help us to differentiate these similar entities [74]. In DH, granular IgA deposition at the tips of dermal papillae is pathognomonic. In LABD, linear deposition of IgA is observed. Sometimes, in less than 5% of the patients, the granular IgA deposits in DH along the basement membrane can be evaluated as linear by mistake [3]. In Japanese patients, IgA deposition in a fibrillary pattern can also be seen [75]. The immunological deposits are not affected after pharmacological therapy. İnstead, the deposits diminish on a gluten-free diet (GFD) [76]. It must be kept in mind that IgA deposition is best seen in normal-appearing perilesional skin rather than in the lesional skin [77]. Warren et al. reported that in 35–40% of the individuals with

DH, the histopathological findings are not demonstrative enough, i.e. sometimes the only finding is the perivascular lymphocytic infiltrate and/or slight dermal papillary inflammation [78]. Sometimes, apart from IgA, deposition of granular IgM and C3 at the dermoepidermal junction can also be present [79]. In **Figure 2**, typical deposition of granular IgA is demonstrated.

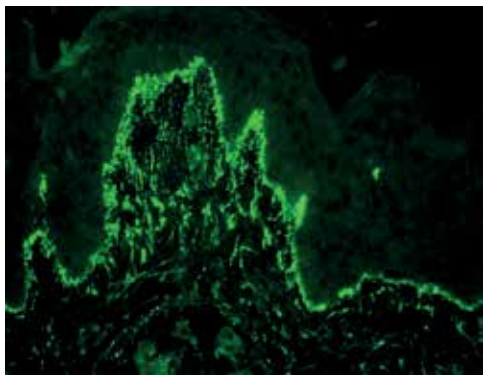

Figure 2. Granular IgA deposits at the tips of the dermal papillae.

Histopathological examination of the intestine is not a must for the diagnosis of DH. But it is a known fact that even in DH patients without gastrointestinal symptoms, the inflammatory changes are present in the small bowel [80].

Serological tests are used in conjunction with pathology and immunopathology. Circulating IgA-type antibodies against endomysium are detected in both DH and CD. Endomysium is the loose connective tissue surrounding muscle fibers. This test is based on indirect immunofluorescence with monkey esophagus as the substrate [81]. IgA-type anti-tTG testing has high specificity and sensitivity and can be used to differentiate DH from LABD, in case of necessity, showing the mucosal damage [82]. Anti-eTG testing has high sensitivity and even higher specificity in diagnosis of DH. Both the levels of anti-tTG and anti-eTG reflect the level of intestinal damage. Any individual on a strict GFD shows low levels of antiendomysial, anti-tTG, and anti-eTG antibodies. Based on this, these antibodies can be used to evaluate the adherence to GFD [65]. In CD, selective IgA deficiency is seldom seen, which causes a possible delay in the diagnosis of the disease. But this is not the case for DH, i.e. IgA deficiency is not common in DH [83]. Antibodies such as antigliadin, antireticulina, antineoepitope tTG, and anti-GAF3X are also found in DH [84–86].

In individuals with DH, D-xylose absorption test is deteriorated in 10–33% of the cases. Iron deficiency anemia and megaloblastic anemia can also help to diagnose in suspicious cases [87].

Genetic testing also can be used when needed for a proper diagnosis. The absence of HLA-DQ2 and HLA-DQ8 alleles, mostly, gives the idea that the individual is unlikely to have DH. But the positivity of these alleles does not always mean that the patient has DH, because these alleles can be positive in normal population frequently [74].

Antiga and Caproni proposed a diagnostic algorithm in DH. According to this algorithm, in case of typical DIF findings and anti-tTG positivity, the diagnosis is certain. In a case with

typical DIF findings but anti-tTG negativity, HLA testing is suggested. If HLA-DQ2 and HLA-DQ8 are negative, DH is excluded. If the alleles are positive, other mentioned antibodies can be checked and intestinal biopsy can be performed. In case of DIF negativity and anti-tTG positivity, HLA testing is recommended. If negative, DH can be excluded, but if positive, a new biopsy for immunofluorescence is recommended. In individuals who are negative for both DIF and anti-tTG, DH can be excluded [1].

6. Differential diagnosis

DH should be differentiated from other bullous skin disorders (such as linear IgA bullous dermatitis and bullous pemphigoid), urticaria, atopic dermatitis, nummular dermatitis, contact dermatitis, and scabies. Linear IgA bullous dermatitis (LABD) has clinical features similar to DH. Larger bullae and "crown of jewels" appearance of the lesions are characteristics of LABD. "Linear" versus "granular" deposition on direct immunofluorescence is the best way to differentiate these two entities. An oil preparation will help to distinguish scabies from DH. Histopathological examination will help to rule out the other dermatoses. **Table 2** summarizes the differential diagnostic features of DH, LABD, and bullous pemphigoid.

	DH	LABD	BP
Lesion appearance	Excoriated papules, vesicles that coalesce	Small vesicles and/or large bullae	Tense bullae
Distribution	Extensor and symmetrical	Extensor and symmetrical	Trunk, extremities
Histopathology	Subepidermal bullae, neutrophils	Subepidermal bullae, neutrophils	Subepidermal bullae, sometimes eosinophils
Direct IF	Granular IgA in dermal papillae	Linear IgA at basement membrane	Linear IgG and C3 at basement membrane
Indirect IF	Mostly (−)	Linear IgA at BMZ	Linear IgG at BMZ
GIS involvement	>90%	Mostly (−)	(−)
Response to dapsone	Excellent	Good	Minimal

Table 2. Differential diagnostic features of DH (dermatitis herpetiformis), LABD (linear IgA bullous dermatitis), and BP (bullous pemphigoid).

7. Treatment

Gluten-free diet (GFD) is a must in the treatment of DH [88]. With GFD, not only the skin lesions resolve but also the pathological findings in intestine improve [89]. The IgA deposits disappear slowly and several years may be necessary for complete resolution. Ingestion of gluten leads to immediate deposition of IgA in the skin and polymorphic eruption arises thereafter [90]. It is tough to stick to GFD. Thus, consultation with a dietician may be necessary and

helpful. Cereals (wheat, barley, and rye) and products containing cereals are rich in gluten [23]. GFD also decreases the malabsorption associated with gluten intolerance. GFD is also thought to minimize the risk of lymphoma, which is believed to be caused by continuous antigenic stimulation [91]. On GFD, gastrointestinal symptoms respond first; later on, the skin lesions respond. In the absence of an additional pharmacological therapy, it may take several years for the cutaneous lesions to disappear [65].

There are few studies that showed cases of DH refractory to GFD. In 2016, Hervonen et al. reported 7 cases out of 403 (1.7%) who were refractory to GFD [92]. In another study, this ratio was nearly 7% [88].

In terms of pharmacotherapy, sulfones like dapsone and sulfapyridine, are accepted as golden standard. These drugs suppress the cutaneous disease immediately [93, 94]. Dapsone is an anti-inflammatory and antibacterial drug which, downregulates neutrophil chemotaxis. As a result, tissue damage, triggered by neutrophils and eosinophils, is inhibited [95, 96]. Skin manifestations are relieved in a few days after dapsone initiation [97]. Usually 25–200 mg/day of dapsone is necessary to control the disease. It has been shown that dapsone alone does not improve the gastrointestinal disease. Therefore, combination of dapsone and GFD is considered as the mainstay of the treatment of DH. Some authors claim that upon strict GFD the dosage of dapsone can be lowered in time and even can be discontinued and restarted in times of flares [98].

The possible side effects of dapsone are well known. Some of the known side effects are the hematological ones such as methemoglobinemia [99]. Methemoglobinemia causes insufficient oxygen to the tissues and manifests by cyanosis, grayish-blue color, weakness, nausea, tachycardia, and abdominal pain [54]. Close follow-up is necessary to rule out this side effect, especially at the beginning of the therapy. To decrease the possibility of methemoglobinemia, cimetidine and/or vitamin E supplement can be prescribed [50]. Patients with glucose-6-phosphate dehydrogenase (G6PD) are more likely to develop hemolysis [100]. The dosage of dapsone must be lowered in these patients. Agranulocytosis is a rare but serious complication and is almost always seen at the beginning of the therapy [101]. Systemic drug hypersensitivity syndrome is another side effect of dapsone treatment, which must also be kept in mind [102]. The sulfone syndrome is seen in the first 2 months of the treatment. Exfoliative dermatitis, fever, lymphadenopathy, hepatitis, vomiting, and hemolysis are independent from the dosage [103, 104]. **Table 3** summarizes the possible side effects of dapsone.

Sulfapyridine, which is the metabolite of both sulfasalazine and sulfamethoxypyridazine, is another therapeutic option in the treatment of DH. The mechanism of action is similar to that of dapsone [105].

Systemic steroids are usually reported to be useless in the treatment of DH [92]. In some instances, potent topical steroids can be used to relieve pruritus [106]. Topical steroids must be used during the acute stage together with the above-mentioned systemic agents.

Tetracycline and nicotinamide combination, colchicine, heparin, and cyclosporine are reported to be effective in the treatment of DH. But there are mostly limited case reports about these treatment options and they need further, large studies [107–109]. Sacchidanand, in 2003, reported good results in DH patients with dexamethasone-cyclophosphamide pulse therapy [110]. Topical dapsone, mycophenolate, and rituximab have also been used for the treatment of DH with variable results [111, 112].

Adverse effects of dapsone	
Blood abnormality	Hemolytic anemia
	Methemoglobinemia
	Agranulocytosis
	Leukopenia
Gastrointestinal side effects	Nausea
	Hepatitis
	Cholestasis
	Hypoalbuminemia
Neurological side effects	Headache
	Peripheral neuropathy
	Dizziness
	Insomnia
	Psychosis
Cutaneous reactions	Maculopapular eruption
	Urticarial reaction
	Fixed drug eruption
	Erythrodermia
	Stevens-Johnson syndrome
	Phototoxicity
	Drug-induced lupus erythematosus
Dapsone hypersensitivity	Hepatitis
	Fatigue
	Anorexia
	Lymphadenopathy

Table 3. The side effects of dapsone.

DH has a chronic nature with remissions and flares. That is why close consultation, long-term GFD, and pharmacological treatment are necessary. In the course of the disease, regular screening for other autoimmune diseases and neoplastic conditions is generally recommended. Blood samples should be taken, at regular intervals, to monitor the possible side effects of the drugs. Anti-tTG and anti-eTG IgA levels can be used to evaluate the adherence of the patients to GFD.

Spontaneous remissions that last months or years are rarely reported. A spontaneous remission is mentioned when there are no lesions for at least 6 months without adherence to GFD [42].

8. Childhood dermatitis herpetiformis

DH, in childhood, resembles the disease of the adulthood with some exceptional features. DH is most commonly seen between the ages of 2 and 7. Girls and boys are equally affected [113]. DH in childhood has an insidious course. It has a long period of pruritus, which is lesion free. The lesions are usually scattered in an asymmetric manner in contrast to adulthood form, which tends to coalesce [114]. Facial lesions are more common in childhood. Palmar linear petechiae and bullae are mostly seen in the childhood form. Chronic urticarial lesions, chronic dermatitis, and hemorrhagic bullae can accompany the classical lesions [48]. Aforementioned enamel defects, oral erosions, and chronic diarrhea can also be seen in the affected children [52, 53, 115].

Interestingly, children with DH can respond to topical steroid treatment initially. This response, at the beginning, diminishes in time [116]. Dapsone is the golden standard in terms of treatment. About 2 mg/kg/day is generally enough to control the disease. The response starts in 72 hours. After satisfactory response, the dosage can be lowered. The second choice is sulfapyridine at a dose of 35–70 mg/kg/day [96].

9. Conclusion

Dermatitis herpetiformis, when undiagnosed, is a distracting disease for the patient with its chronic nature and the itching. In case of a polymorphic eruption and pruritus, DH must come to mind. After proper history taking, physical examination, and laboratory investigations, its diagnosis is, mostly, easy. GFD and dapsone ensure an untroubled life for the patient. But we should, always, be aware of the possible side effects of the therapy.

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References

[1] Antiga E, Caproni M. The diagnosis and treatment of dermatitis herpetiformis. Clinical, Cosmetic and Investigational Dermatology. 2015;**13**(8):257-265. DOI: 10.2147/CCID.S69127

[2] Mendes FBR, Hissa-Elian A, de Abreu MAMM, Gonçalves VS. Review: Dermatitis herpetiformis. Anais Brasileiros de Dermatologia. 2013;**88**(4):594-599. DOI: 10.1590/abd1806-4841.20131775

[3] Caproni M, Antiga E, Melani L, Fabbri P, Italian Group for Cutaneous Immunopathology. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. Journal of the European Academy of Dermatology and Venereology. 2009;**23**(6):633-638. DOI: 10.1111/j.1468-3083.2009.03188.x

[4] Collin P, Reunala T, Rasmussen M, Kyronpalo S, Pehkonen E, et al. High incidence and prevalence of adult coeliac disease. Augmented diagnostic approach. Scandinavian Journal of Gastroenterology. 1997;**32**(11):1129-1133. DOI: 10.3109/00365529709002992

[5] Fry L. Dermatitis herpetiformis. Baillière's Clinical Gastroenterology. 1995;**9**(2):371-393. DOI: 10.1016/0950-3528(95)90036-5

[6] Ohata C, Ishii N, Hamada T, Shimomura Y, Niizeki H, et al. Distinct characteristics in Japanese dermatitis herpetiformis: A review of all 91 Japanese patients over the last 35 years. Clinical & Developmental Immunology. 2012;**2012**:1-9. DOI: 10.1155/2012/562168

[7] Salmi TT, Hervonen K, Kautiainen H, Collin P, Reunala T. Prevalence and incidence of dermatitis herpetiformis: A 40-year prospective study from Finland. The British Journal of Dermatology. 2011;**165**(2):354-359. DOI: 10.1111/j.1365-2133.2011.10385.x

[8] Gawkrodger DJ, Vestey JP, O'Mahony S, Marks JM. Dermatitis herpetiformis and established coeliac disease. The British Journal of Dermatology. 1993;**129**(6):694-695. DOI: 10.1111/j.1365-2133.1993.tb03333.x

[9] Shibahara M, Nanko H, Shimizu M, Kanda N, Kubo M, et al. Dermatitis herpetiformis in Japan: An update. Dermatology. 2002;**204**(1):37-42. DOI: 10.1159/000051808

[10] Antiga E, Verdelli A, Calabrò A, Fabbri P, Caproni M. Clinical and immunopathological features of 159 patients with dermatitis herpetiformis: An Italian experience. Giornale Italiano di Dermatologia e Venereologia. 2013;**148**(2):163-169. DOI: 10.2147/CCID.S69127

[11] Llorente-Alonso MJ, Fernández-Acenero MJ, Sebastián M. Gluten intolerance: Sex and age-related features. Canadian Journal of Gastroenterology. 2006;**20**(11):719-722

[12] Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Journal of the American Academy of Dermatology. 2011;**64**(6):1017-1024. DOI: 10.1016/j.jaad.2010.09.777

[13] Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, et al. Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. The Journal of Investigative Dermatology. 2000;**115**(6):990-993. DOI: 10.1046/j.1523-1747.2000.00172.x

[14] Hervonen K, Hakanen M, Kaukinen K, Collin P, Reunala T. First-degree relatives are frequently affected in coeliac disease and dermatitis herpetiformis. Scandinavian Journal of Gastroenterology. 2002;**37**(1):51-55. DOI: 10.1080/003655202753387356

[15] Alonso-Llamazares J, Gibson LE, Rogers RS. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: Review of the Mayo Clinic experience. International Journal of Dermatology. 2007;**46**(9):910-919. DOI: 10.1111/j.1365-4632.2007.03214.x

[16] Amundsen SS, Monsuur AJ, Wapenaar MC, Lie BA, Ek J, et al. Association analysis of MYO9B gene polymorphisms with celiac disease in a Swedish/Norwegian cohort. Human Immunology. 2006;**67**(4-5):341-345. DOI: 10.1016/j.humimm.2006.03.020

[17] Koskinen LLE, Korponay-Szabo IR, Viiri K, Juuti-Uusitalo K, Kaukinen K, et al. Myosin IXB gene region and gluten intolerance: Linkage to coeliac disease and a putative dermatitis herpetiformis association. Journal of Medical Genetics. 2007;**45**(4):222-227. DOI: 10.1136/jmg.2007.053991

[18] Hunt KA, Monsuur AJ, McArdle WL, Kumar PJ, Travis SP, et al. Lack of association of MYO9B genetic variants with coeliac disease in a British cohort. Gut. 2006;**55**(7):969-972. DOI: 10.1136/gut.2005.086769

[19] Spurkland A, Ingvarsson G, Falk ES, Knutsen I, Sollid LM, et al. Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1*0501, beta 1*02) or the HLA-DQ (alpha 1*03, beta 1*0302) heterodimers. Tissue Antigens. 1997;**49**(1):29-34. DOI: 10.1111/j.1399-0039.1997.tb02706.x

[20] Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nature Medicine. 1997;**3**(7):797-801. DOI: 10.1038/nm0797-797

[21] Caputo I, Barone MV, Martucciello S, Lepretti M, Esposito C. Tissue transglutaminase in celiac disease: Role of autoantibodies. Amino Acids. 2009;**36**(4):693-699. DOI: 10.1007/s00726-008-0120-z

[22] Schuppan D, Dieterich W, Ehnis T, Bauer M, Donner P, et al. Identification of the autoantigen of celiac disease. Annals of the New York Academy of Sciences. 1998;**859**:121-126. DOI: 10.1053/gast.2000.8521

[23] Kárpáti S. Dermatitis herpetiformis: Close to unravelling a disease. Journal of Dermatological Science. 2004;**34**(2):83-90. DOI: 10.1016/j.jdermsci.2003.11.004

[24] Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AVS. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. Nature Medicine. 2000;**6**(3):337-342. DOI: 10.1038/73200

[25] Molberg O, Mcadam SN, Körner R, Quarsten H, Kristiansen C, et al. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. Nature Medicine. 1998;**4**(6):713-717

[26] Zone JJ, Egan CA, Taylor TB, Meyer LJ. IgA autoimmune disorders: Development of a passive transfer mouse model. The Journal of Investigative Dermatology. Symposium Proceedings. 2004;**9**(1):47-51. DOI: 10.1111/j.1087-0024.2004.00840.x

[27] Hull CM, Liddle M, Hansen N, Meyer LJ, Schmidt L, et al. Elevation of IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis. The British Journal of Dermatology. 2008;**159**(1):120-124. DOI: 10.1111/j.1365-2133.2008.08629.x

[28] Kawana S, Segawa A. Confocal laser scanning microscopic and immunoelectron microscopic studies of the anatomical distribution of fibrillar IgA deposits in dermatitis herpetiformis. Archives of Dermatology. 1993;**129**(4):456-459. DOI: 10.1001/archderm.1993.01680250068008

[29] Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. The Journal of Experimental Medicine. 2002;**195**(6):747-757. DOI: 10.2340/00015555-2162

[30] Reunala TL. Dermatitis herpetiformis. Clinics in Dermatology. 2001;**19**(6):728-736. DOI: 10.1016/S0738-081X(00)00184-X

[31] Hitomi K. Transglutaminases in skin epidermis. European Journal of Dermatology. 2005;**15**(5):313-319

[32] Lorand L, Graham RM. Transglutaminases: Crosslinking enzymes with pleiotropic functions. Nature Reviews. Molecular Cell Biology. 2003;**4**(2):140-156. DOI: 10.1038/nrm1014

[33] Jaskowski TD, Hamblin T, Wilson AR, Hill HR, Book LS, et al. IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis and pediatric celiac disease. The Journal of Investigative Dermatology. 2009;**129**(11):2728-2730. DOI: 10.1038/jid.2009.142

[34] Rose C, Bröcker E-B, Zillikens D. Clinical, histological and immunpathological findings in 32 patients with dermatitis herpetiformis Duhring. Journal der Deutschen Dermatologischen Gesellschaft. 2009;**8**(4):265-270, 265-271. DOI: 10.1111/j.1610-0387.2009.07292.x

[35] Leonard J, Haffenden G, Tucker W, Unsworth J, Swain F, et al. Gluten challenge in dermatitis herpetiformis. The New England Journal of Medicine. 1983;**308**(14):816-819. DOI: 10.1056/NEJM198304073081406

[36] Charlesworth EN, Backe JT, Letter GRL. Iodide-induced immunofluorescence in dermatitis herpetiformis. Archives of Dermatology. 1976;**112**(4):555. DOI: 10.1001/archderm.1976.01630280073025

[37] Katz KA, Roseman JE, Roseman RL, Katz SI. Dermatitis herpetiformis flare associated with use of triiodomethane packing strips for alveolar osteitis. Journal of the American Academy of Dermatology. 2009;**60**(2):352-353. DOI: 10.1016/j.jaad.2008.08.041

[38] Austin AS, Logan RFA, Thomason K, Holmes GKT. Cigarette smoking and adult coeliac disease. Scandinavian Journal of Gastroenterology. 2002;**37**(8):978-982. DOI: 10.1186/1471-230X-14-120

[39] Snook JA, Dwyer L, Lee-Elliott C, Khan S, Wheeler DW, et al. Adult coeliac disease and cigarette smoking. Gut. 1996;**39**(1):60-62. DOI: 10.1136/gut.39.1.60

[40] Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: A guide for dermatologists. American Journal of Clinical Dermatology. 2003;**4**(1):13-20

[41] Junkins-Hopkins JM. Dermatitis herpetiformis: Pearls and pitfalls in diagnosis and management. Journal of the American Academy of Dermatology. 2010;**63**(3):526-528. DOI: 10.1016/j.jaad.2010.05.027

[42] Kárpáti S. An exception within the Group of autoimmune blistering diseases: Dermatitis herpetiformis, the gluten-sensitive dermopathy. Immunology and Allergy Clinics of North America. 2012;**32**(2):255-262. DOI: 10.1016/j.iac.2012.04.005

[43] Kosann MK. Dermatitis herpetiformis. Dermatology Online Journal. 2003;**9**(4):8. DOI: 10.1590/abd1806-4841.20131775

[44] Hofmann S, Nashan D, Bruckner-Tuderman L. Petechiae on the fingertips as presenting symptom of dermatitis herpetiformis Duhring. Journal of the European Academy of Dermatology and Venereology. 2009;**23**(6):732-733. DOI: 10.1111/j.1468-3083.2009.03200.x

[45] Marks R, Jones EW. Purpura in dermatitis herpetiformis. The British Journal of Dermatology. 1971;**84**(4):386-388. DOI: 10.2147/CCID.S69127

[46] Naylor E, Atwater A, Selim MA, Hall R, Puri PK. Leukocytoclastic vasculitis as the presenting feature of dermatitis herpetiformis. Archives of Dermatology. 2011;**147**(11):1313. DOI: 10.1001/archdermatol.2011.293

[47] Ohshima Y, Tamada Y, Matsumoto Y, Hashimoto T. Dermatitis herpetiformis Duhring with palmoplantar keratosis. The British Journal of Dermatology. 2003;**149**(6):1300-1302. DOI: 10.1111/j.1365-2133.2003.05660.x

[48] Powell GR, Bruckner AL, Weston WL. Dermatitis herpetiformis presenting as chronic urticaria. Pediatric Dermatology. 2004;**21**(5):564-567. DOI: 10.1111/j.0736-8046.2004.21509.x

[49] Saito M, Böer A, Ishiko A, Nishikawa T. Atypical dermatitis herpetiformis: A Japanese case that presented with initial lesions mimicking prurigo pigmentosa. Clinical and Experimental Dermatology. 2006;**31**(2):290-291. DOI: 10.1111/j.1365-2230.2005.02009.x

[50] Nicolas MEO, Krause PK, Gibson LE, Murray JA. Dermatitis herpetiformis. International Journal of Dermatology. 2003;**42**(8):588-600. DOI: 10.1155/2012/239691

[51] Aine L, Mäki M, Reunala T. Coeliac-type dental enamel defects in patients with dermatitis herpetiformis. Acta Dermato-Venereologica. 1992;**72**(1):25-27. DOI: 10.3109/07853899608999067

[52] Aine L, Reunala T, Mäki M. Dental enamel defects in children with dermatitis herpetiformis. The Journal of Pediatrics. 1991;**118**(4 Pt 1):572-574

[53] Mäki M, Aine L, Lipsanen V, Koskimies S. Dental enamel defects in first-degree relatives of coeliac disease patients. Lancet (London, England). 1991;**337**(8744):763-764. DOI: 10.1016/0140-6736(91)91375-5

[54] Holtmeier W, Pfänder M, Zollner TM, Kaufmann R, Caspary WF. Distinct TCR delta repertoires are present in the cutaneous lesions and inflamed duodenum of patients with dermatitis herpetiformis. Experimental Dermatology. 2002;**11**(6):527-531. DOI: 10.1034/j.1600-0625.2002.110605.x

[55] Rubio-Tapia A, Murray JA. Celiac disease. Current Opinion in Gastroenterology. 2010;**26**(2):116-122. DOI: 10.1097/MOG.0b013e3283365263

[56] Gaspari AA, Huang CM, Davey RJ, Bondy C, Lawley TJ, et al. Prevalence of thyroid abnormalities in patients with dermatitis herpetiformis and in control subjects with HLA-B8/−DR3. The American Journal of Medicine. 1990;**88**(2):145-150. DOI: 10.1016/0002-9343(90)90464-O

[57] Kaplan RP, Callen JP. Overlapping cutaneous disorders related to dermatitis herpetiformis. Clinics in Dermatology. 1991;**9**(3):361-368. DOI: 10.1016/0738-081X(91)90027-I

[58] Zettinig G, Weissel M, Flores J, Dudczak R, Vogelsang H. Dermatitis herpetiformis is associated with atrophic but not with goitrous variant of Hashimoto's thyroiditis. European Journal of Clinical Investigation. 2000;**30**(1):53-57. DOI: 10.1046/j.1365-2362.2000.00590.x

[59] Hervonen K, Viljamaa M, Collin P, Knip M, Reunala T. The occurrence of type 1 diabetes in patients with dermatitis herpetiformis and their first-degree relatives. The British Journal of Dermatology. 2004;**150**(1):136-138. DOI: 10.1111/j.1365-2133.2004.05642.x

[60] Neuhausen SL, Steele L, Ryan S, Mousavi M, Pinto M, et al. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. Journal of Autoimmunity. 2008;**31**(2):160-165. DOI: 10.1016/j.jaut.2008.06.001

[61] Amato L, Gallerani I, Fuligni A, Mei S, Fabbri P. Dermatitis herpetiformis and vitiligo: Report of a case and review of the literature. The Journal of Dermatology. 2000;**27**(7):462-466. DOI: 10.1111/j.1346-8138.2000.tb02207.x

[62] Karabudak O, Dogan B, Yildirim S, Harmanyeri Y, Anadolu-Brasie R. Dermatitis herpetiformis and vitiligo. Journal of the Chinese Medical Association. 2007;**70**(11):504-506. DOI: 10.1016/S1726-4901(08)70049-2

[63] Reunala T, Salmi J, Karvonen J. Dermatitis herpetiformis and celiac disease associated with Addison's disease. Archives of Dermatology. 1987;**123**(7):930-932. DOI: 10.1001/archderm.1987.01660310098023

[64] Stavropoulos P, Moustou A-EI, Tsiougou M, Avgerinou G, Chatziolou E, et al. Might dermatitis herpetiformis be associated with discoid lupus erythematosus? Journal of the European Academy of Dermatology and Venereology. 2008;**22**(6):749-750. DOI: 10.1111/j.1468-3083.2007.02443.x

[65] Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Journal of the American Academy of Dermatology. 2011;**64**(6):1027-1033. DOI: 10.1016/j.jaad.2010.09.776

[66] Hervonen K, Vornanen M, Kautiainen H, Collin P, Reunala T. Lymphoma in patients with dermatitis herpetiformis and their first-degree relatives. The British Journal of Dermatology. 2005;**152**(1):82-86. DOI: 10.1111/j.1365-2133.2005.06345.x

[67] Nassiri M, Robertson MJ, Hertzberg L, Czader MB. Primary effusion anaplastic large cell lymphoma in a patient with long-standing dermatitis herpetiformis and celiac disease. Annals of Hematology. 2013;**92**(2):279-281. DOI: 10.1007/s00277-012-1554-7

[68] Sigurgeirsson B, Agnarsson BA, Lindelöf B. Risk of lymphoma in patients with dermatitis herpetiformis. BMJ. 1994;**308**(6920):13-15. DOI: 10.1136/bmj.308.6920.13

[69] Viljamaa M, Kaukinen K, Pukkala E, Hervonen K, Reunala T, et al. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. Digestive and Liver Disease. 2006;**38**(6):374-380. DOI: 10.1016/j.dld.2006.03.002

[70] Reunala T, Salmi T, Hervonen K. Dermatitis herpetiformis: Pathognomonic transglutaminase IgA deposits in the skin and excellent prognosis on a gluten-free diet. Acta Dermato-Venereologica. 2015;**95**(8):917-922. DOI: 10.2340/00015555-2162

[71] Lewis NR, Logan RFA, Hubbard RB, West J. No increase in risk of fracture, malignancy or mortality in dermatitis herpetiformis: A cohort study. Alimentary Pharmacology & Therapeutics. 2008;**27**(11):1140-1147. DOI: 10.1111/j.1365-2036.2008.03660.x

[72] Arundhathi S, Raghunatha S, Mahadeva KC. A cross-sectional study of clinical, histopathological and direct immunofluorescence spectrum of vesiculobullous disorders. Journal of Clinical and Diagnostic Research. 2013;**7**(12):2788-2792. DOI: 10.7860/JCDR/2013/7019.3760

[73] Pierard J. Concerning the histological aspect of the erythematous plagues of Duhring's herpetiform dermatitis. Annales De Dermatologie Et De Syphiligraphie. 1986;**90**:121-133

[74] Zone JJ. Skin manifestations of celiac disease. Gastroenterology. 2005;**128**(4 Suppl 1):S87-S91. DOI: 10.1053/j.gastro.2005.02.026

[75] Ko CJ, Colegio OR, Moss JE, McNiff JM. Fibrillar IgA deposition in dermatitis herpetiformis—An underreported pattern with potential clinical significance. Journal of Cutaneous Pathology. 2010;**37**(4):475-477. DOI: 10.1111/j.1600-0560.2009.01472.x

[76] Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Archives of Dermatology. 1996;**132**(8):912-918. DOI: 10.1001/archderm.1996.03890320060010

[77] Beutner EH, Chorzelski TP, Reunala TL, Kumar V. Immunopathology of dermatitis herpetiformis. Clinics in Dermatology. 1991;**9**(3):295-311. DOI: 10.1016/0738-081X(91)90021-C

[78] Warren SJP, Cockerell CJ. Characterization of a subgroup of patients with dermatitis herpetiformis with nonclassical histologic features. The American Journal of Dermatopathology. 2002;**24**(4):305-308

[79] Barnadas MA. Dermatitis Herpetiformis. The American Journal of Dermatopathology. 2016;**38**(4):283-288. DOI: 10.1097/DAD.0000000000000420

[80] Nakajima K. Recent advances in dermatitis herpetiformis. Clinical & Developmental Immunology. 2012;**2012**:914162. DOI: 10.1155/2012/914162

[81] Dieterich W, Schuppan D, Laag E, Reunala T, Kárpáti S, et al. Antibodies to tissue transglutaminase as serologic markers in patients with dermatitis herpetiformis. The Journal of Investigative Dermatology. 1999;**113**(1):133-136. DOI: 10.1046/j.1523-1747.1999.00627.x

[82] Rose C, Dieterich W, Bröcker EB, Schuppan D, Zillikens D. Circulating autoantibodies to tissue transglutaminase differentiate patients with dermatitis herpetiformis from those with linear IgA disease. Journal of the American Academy of Dermatology. 1999;**41**(6):957-961. DOI: 10.1016/S0190-9622(99)70253-7

[83] Samolitis NJ, Hull CM, Leiferman KM, Zone JJ. Dermatitis herpetiformis and partial IgA deficiency. Journal of the American Academy of Dermatology. 2006;**54**(5):S206-S209. DOI: 10.1016/j.jaad.2005.06.033

[84] Kasperkiewicz M, Dähnrich C, Probst C, Komorowski L, Stöcker W, et al. Novel assay for detecting celiac disease–associated autoantibodies in dermatitis herpetiformis using deamidated gliadin-analogous fusion peptides. Journal of the American Academy of Dermatology. 2012;**66**(4):583-588. DOI: 10.1016/j.jaad.2011.02.025

[85] Lytton SD, Antiga E, Pfeiffer S, Matthias T, Szaflarska-Poplawska A, et al. Neo-epitope tissue transglutaminase autoantibodies as a biomarker of the gluten sensitive skin disease—Dermatitis herpetiformis. Clinica Chimica Acta. 2013;**415**:346-349. DOI: 10.1016/j.cca.2012.10.051

[86] Sitaru C, Zillikens D. Mechanisms of blister induction by autoantibodies. Experimental Dermatology. 2005;**14**(12):861-875. DOI: 10.1111/j.1600-0625.2005.00367.x

[87] Griffiths CE, Menzies IS, Barrison IG, Leonard JN, Fry L. Intestinal permeability in dermatitis herpetiformis. The Journal of Investigative Dermatology. 1988;**91**(2):147-149. DOI: 10.1111/1523-1747.ep12464390

[88] Garioch JJ, Lewis HM, Sargent SA, Leonard JN, Fry L. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. The British Journal of Dermatology. 1994;**131**(4):541-545. DOI: 10.1111/j.1365-2133.1994.tb08557.x

[89] Fry L, Leonard JN, Swain F, Tucker WF, Haffenden G, et al. Long term follow-up of dermatitis herpetiformis with and without dietary gluten withdrawal. The British Journal of Dermatology. 1982;**107**(6):631-640. DOI: 10.1111/j.1365-2133.1982.tb00520.x

[90] Kilander AF, Gillberg RE, Kastrup W, Mobacken H, Nilsson LA. Serum antibodies to gliadin and small-intestinal morphology in dermatitis herpetiformis. A controlled clinical study of the effect of treatment with a gluten-free diet. Scandinavian Journal of Gastroenterology. 1985;**20**(8):951-958. DOI: 10.3109/00365528509088854

[91] Lewis HM, Renaula TL, Garioch JJ, Leonard JN, Fry JS, et al. Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. The British Journal of Dermatology. 1996;**135**(3):363-367. DOI: 10.1046/j.1365-2133.1996.d01-1005.x

[92] Hervonen K, Salmi T, Ilus T, Paasikivi K, Vornanen M, et al. Dermatitis herpetiformis refractory to gluten-free dietary treatment. Acta Dermato-Venereologica. 2016;**96**(1):82-86. DOI: 10.2340/00015555-2184

[93] Egan CA, O'Loughlin S, Gormally S, Powell FC. Dermatitis herpetiformis: A review of fifty-four patients. Irish Journal of Medical Science. 1997;**166**(4):241-244. DOI: 10.1007/BF02944243

[94] Leonard JN, Fry L. Treatment and management of dermatitis herpetiformis. Clinics in Dermatology. 1991;**9**(3):403-408. DOI: 10.2147/CCID.S69127

[95] Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: Inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. Journal of Leukocyte Biology. 1997;**62**(6):827-836

[96] Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: Overview and update. Journal of the American Academy of Dermatology. 2001;**45**(3):420-434. DOI: 10.1067/mjd.2001.114733

[97] Booth SA, Moody CE, Dahl MV, Herron MJ, Nelson RD. Dapsone suppresses integrin-mediated neutrophil adherence function. The Journal of Investigative Dermatology. 1992;**98**(2):135-140. DOI: 10.1111/1523-1747.ep12555654

[98] Paek SY, Steinberg SM, Katz SI. Remission in dermatitis Herpetiformis. Archives of Dermatology. 2011;**147**(3):301. DOI: 10.1001/archdermatol.2010.336

[99] Sunilkumar MN, Ajith TA, Parvathy VK. Acute dapsone poisoning in a 3-year-old child: Case report with review of literature. World Journal of Clinical Cases. 2015;**3**(10):911-914. DOI: 10.12998/wjcc.v3.i10.911

[100] Luzzatto L, Seneca E. G6PD deficiency: A classic example of pharmacogenetics with on-going clinical implications. British Journal of Haematology. 2014;**164**(4):469-480. DOI: 10.1111/bjh.12665

[101] Potočnjak I, Likić R, Šimić I, Juričić Nahal D, Cegec I, et al. Dapsone-induced agranulocytosis-possible involvement of low-activity N-acetyltransferase 2. Fundamental & Clinical Pharmacology. 2017;**31**(5):580-586. DOI: 10.1111/fcp.12287

[102] Choi SY, Hwang HY, Lee JH, Park JS, Jang MS. Severe dapsone hypersensitivity syndrome in a child. Korean Journal of Pediatrics. 2013;**56**(6):260. DOI: 10.3345/kjp.2013.56.6.260

[103] Glied M, Rico MJ. Treatment of autoimmune blistering diseases. Dermatologic Clinics. 1999;**17**(2):431-440

[104] Sener O, Doganci L, Safali M, Besirbellioglu B, Bulucu F, et al. Severe dapsone hypersensitivity syndrome. Journal of Investigational Allergology & Clinical Immunology. 2006;**16**(4):268-270

[105] Cardones ARG, Hall RP. Management of dermatitis herpetiformis. Dermatologic Clinics. 2011;**29**(4):631-635. DOI: 10.1016/j.det.2011.06.015

[106] Björnberg A, Hellgren L. Topical treatment of dermatitis herpetiformis with betamethasone-17-valerate and fluocinolone acetonide. Acta Allergologica. 1966;**21**(6):471-472. DOI: 10.1111/j.1398-9995.1966.tb03165.x

[107] Famaey JP. Colchicine in therapy. State of the art and new perspectives for an old drug. Clinical and Experimental Rheumatology. 1988;**6**(3):305-317

[108] Shah SA, Ormerod AD. Dermatitis herpetiformis effectively treated with heparin, tetracycline and nicotinamide. Clinical and Experimental Dermatology. 2000;**25**(3):204-205. DOI: 10.1046/j.1365-2230.2000.00615.x

[109] Stenveld HJ, Starink TM, van Joost T, Stoof TJ. Efficacy of cyclosporine in two patients with dermatitis herpetiformis resistant to conventional therapy. Journal of the American Academy of Dermatology 1993;**28**(6):1014-1015. DOI:10.1016/S0190-9622(08)80657-3

[110] Sacchidanand S, Hiremath NC, Natraj HV, Revathi TN, Rani S, et al. Dexamethasone-cyclophosphamide pulse therapy for autoimmune-vesiculobullous disorders at Victoria hospital, Bangalore. Dermatology Online Journal. 2003;**9**(5):2. DOI: 10.4103/0378-6323.53133

[111] Albers LN, Zone JJ, Stoff BK, Feldman RJ. Rituximab treatment for recalcitrant dermatitis Herpetiformis. JAMA Dermatology. 2017;**153**(3):315. DOI: 10.1001/jamadermatol.2016.4676

[112] Kotze LM da S. Dermatitis herpetiformis, the celiac disease of the skin! Arquivos de Gastroenterologia. 2013;**50**(3):231-235. DOI: 10.1590/S0004-28032013000200041

[113] Lemberg D, Day AS, Bohane T. Coeliac disease presenting as dermatitis herpetiformis in infancy. Journal of Paediatrics and Child Health. 2005;**41**:294-296

[114] Medica I, Zmak M, Persic M. Dermatitis herpetiformis in a 30-month-old child. Minerva Pediatrica. 2003;**55**:171-173

[115] Thibaud D, Jourdain JC, Le Lorier B, et al. Herpetiform dermatitis of the infant forming hemorrhagic bullae in diarrhea. Pediatrician. 2001;**8**:1399-1400

[116] Horvath K, Mehta DI. Celiac disease—A worldwide problem. Indian Journal of Pediatrics. 2000;**67**:757-763

Chapter 6

Bullous Systemic Lupus Erythematosus and Cicatricial Pemphigoid

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Additional information is available at the end of the chapter

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Abstract

Bullous systemic lupus erythematosus is a rare distinctive subepidermal bullous disease seen in patients with systemic lupus erythematosus (SLE). It has characteristical clinic, pathologic, and immunologic findings including antibodies to type VII collagen, laminin 332, laminin 331, and bullous pemphigoid antigen 230. Clinical presentation combined with histopathology, immunological testing, and concomitant diagnosis of SLE according to the criteria of American College of Rheumatology, are required to distinguish bullous SLE from these bullous diseases. In patients with bullous SLE, SLE disease progression and complications may be worse. Cicatricial pemphigoid is a chronic subepidermal blistering disease which is characterized by erosive lesions of mucous membranes and skin. Pathogenesis of cicatricial pemphigoid is characterized by linear deposition of Immunoglobulin G, A, or complement 3 along the epithelial basement membrane zone. The main target antigens are bullous pemphigoid antigens 180–230, laminin 331–332, type VII collagen, and β-4 integrin subunit. Cicatricial pemphigoid may lead to serious complications such as blindness and airway obstruction. Herein, clinical, histological, immunopathological features, the diagnosis and treatment of bullous SLE and cicatricial pemphigoid diseases are mentioned to raise awareness among the dermatologists about this important but rare heterogeneous bullous disease.

Keywords: bullous dermatosis, bullous systemic lupus erythematosus, nephritis, cicatricial pemphigoid, mucous membrane pemphigoid, ocular, oral, subepithelial autoimmune disease

1. Bullous systemic lupus erythematosus

1.1. Introduction

It has been reported that numerous cutaneous lesions might be seen in 59–76% of patients with systemic lupus erythematosus (SLE) [1, 2]. But, blistering lesions are relatively

uncommon, which is approximately less than 1% of all cutaneous lesions seen in SLE [2]. Patients with SLE may have intense inflammation and basal vacuolar degeneration that induce blister formation [3]. However, SLE with concomitant separate bullae is rare. Bullous SLE (BSLE) is a heterogeneous disease that has distinctive clinical and histologic features [1].

BSLE is caused by several defined autoantibodies. Primary autoantibodies are anti-type VII collagen antibody [4] and antibodies against laminin (Lam)-332, Lam-331, and bullous pemphigoid (BP) antigen-230 have been identified later [5, 6].

Rupture of blisters leads to skin loss and erosions that cause significant dehydration, loss of electrolytes, and proteins, particularly if there is extensive body surface involvement. Moreover, if the oral mucosa, and gastrointestinal system are affected, the patient may not be able to take adequate food and medication. Thus, these changes cause immunosuppression, and eventually infections and sepsis as well. So, it is important to diagnose and treat carefully all autoimmune bullous dermatoses, as they have fatal complications and morbidities [7].

BSLE is characterized by subepidermal, transient, tense vesiculobullous eruptions located on any area of the body. Contrast to BSLE, in all types of cutaneous lupus erythematosus (CLE), vesiculobullous lesions are typically polycyclic erosions with an advancing blistering border on sun-exposed areas of the body [8–11]. Beyond the clinical presentations, pathogenesis and histopathological features are quite different among those types of diseases. In CLEs, a genetic base originated from variations in multiple loci leads to susceptibility to LE and disease activity is provoked by exogenous or endogenous triggers. The best known trigger is exposure to ultraviolet radiation [8, 12–15]. BSLE is associated with an increased prevalence of the human leukocyte antigen (HLA) class II DR2 haplotype-like SLE. Furthermore, it has also been found that the DR2-associated DRB1*1501 allele can be seen in patients who develop antibodies to type VII collagen [16]. However, triggering factors have not been exactly defined in BSLE [9].

Histologic findings of CLEs such as epidermal atrophy, hydropic changes, apoptotic keratinocytes, and mucin deposits are not expected in BSLE either. Direct immunofluorescence (DIF) study in CLEs and BSLE may be similar while IIF studies show different findings [3, 14]. Thus, differentiation of BSLE from other types of CLEs can be possible based on clinical features, histopathology, and immunohistochemical examinations.

Dermatitis herpetiformis (DH), BP, epidermolysis bullosa acquisita (EBA), and linear immunoglobulin (Ig) A bullous dermatoses (LABD) are included in the differential diagnosis of BSLE due to the presence of similarities in clinic, histology, and immunopathology [17]. Briefly, DH can be excluded by light microscopy and direct immunofluorescence (DIF) method. BSLE, BP, and EBA have similar DIF patterns. Salt-split skin test demonstrates IgG antibodies on the epidermal side (roof pattern) of the split skin in BP unlike EBA and BSLE in which IgG antibodies bind on the dermal side (floor pattern) of the split skin. Thus, differentiation between BSLE and EBA is not possible by demonstration of dermal binding in salt-split skin test. Presence of ACR criteria for the diagnosis of SLE points the way to BSLE [6, 18].

To diagnose BSLE, fulfillment of the criteria of SLE is required. The Systemic Lupus International Collaborating Clinic (SLICC) group recently validated the 1997 American College of Rheumatology (ACR) revised criteria for SLE [19, 20]. Also, a new classification was defined by SLICC group. Misdiagnosis of SLE is less likely to occur through this new classification system. During the vesiculobullous presentation of BSLE, also systemic symptoms of SLE may get worse. Particularly, nephritis has been found associated to BSLE in many cases [12, 21–23]. However, the exact underlying mechanism has not been found yet.

A thorough history, the clinical presentation, fulfilling the criteria of ACR for SLE and histopathological findings along with DIF, IIF, and ELISA can be helpful in diagnosing most cases of BSLE [24].

BSLE lesions are usually recalcitrant to the systemic corticosteroids which are used to treat the other manifestations of SLE [1]. The corner stone treatment of BSLE is dapsone and response is rapid even with small doses [1, 5, 8]. However, sometimes for the patients who fail to respond to dapsone or have intolerance to dapsone or have significant systemic SLE involvement—includes nephritis—other medications such as systemic steroids or other immunomodulatory treatments such as azathioprine, methotrexate, antimalarial agents, mycophenolate mofetil (MMF), rituximab, and intravenous immunoglobulin (IVIG) may be needed [5, 6].

1.2. Epidemiology and history

BSLE is an uncommon, auto-antibody-mediated subepidermal bullous eruption occurring in patients with SLE [4, 5]. BSLE generally affects young females of all races especially in the second to fourth decades of life. There have been some reported cases in older patients or in children as well [10–13, 25]. Female dominance may be related to SLE. Furthermore, there has been no informed race predominance up to now [8].

There have been case reports on SLE presenting with hemorrhagic bullae on sun-exposed areas of the body of patients in the literature as early as in the late nineteenth century. The clinical photographs of a patient were published in 1961 by Tromovitch and Hyman. She was a 26-year-old woman with SLE and had hemorrhagic bullae on the extensor aspects of the arms and legs, which are thought to be bullae of bullous SLE. The histologic examination of the lesion revealed bullae containing polymorphonuclear cells and some lymphocytes. But in that time, DIF method was not available, and so it could not be performed as well [26]. Also, the first well-documented cases of BSLE were published by Hall et al. [27].

1.3. Immunopathogenesis

In BSLE, main autoantibodies are circulating anti-type VII collagen antibodies (noncollagenous domain (NC) 1 and 2). Type VII collagen is found in the basement membrane zone (BMZ) as an important element of anchoring fibrils, and maintains adhesion at the dermoepidermal junction (DEJ). Lam-332, and fibronectin, and especially NC1 domain of type VII collagen play important role in adhesion between the lamina densa, lamina lucida, and keratinocytes. Antibodies against type VII collagen are characteristic for both BSLE and EBA [4, 5].

On the other hand, Chan et al. [6] has described other antigens related to immunopathogenesis of BSLE, which are namely Lam-331, Lam-332, and BP230. Although these molecules have been identified, the exact mechanism of autoimmunity in BSLE has yet to be elucidated, but it is theorized that antibodies to type VII collagen induces epitope spreading which leads to a secondary autoimmune response to the newly exposed targets in BSLE [1, 6, 8].

The NC1 domain of type VII collagen which consists of nine back-to-back homologous fibronectin III-like subdomains and two flanking von Willebrand factor A-like domains, play a role in mediating interactions between type VII collagen and other matrix proteins [28]. The aminoterminal is also termed as cartilage matrix protein and antibodies to this cartilage matrix protein subdomain have been shown to induce dermoepidermal separation *in vivo* [29]. However, the pathogenic relevance of binding of autoantibodies to fibronectin III-like domains which was shown by immunoblotting has not been clarified yet [30]. In both *ex vivo* and *in vivo* studies demonstrated that the Fc portion of the autoantibody, activation of complement and release of elastase and gelatinase B, and reactive oxygen species released from activated neutrophils are important for blister formation in BSLE and EBA [13, 31–33]. As mentioned previously, in addition to complement activation, release of proteases and reactive oxygen species from neutrophils has been shown to be fundamental for dermoepidermal separation induced by autoantibodies to type VII collagen *ex vivo* and *in vivo* in the pathogenesis of BSLE and EBA [11, 12, 20, 31, 32, 34].

An association between susceptibility to LE and autoimmunity to type VII collagen has been suspected for the reason of presence of autoantibodies to type VII collagen are part of the autoantibody repertoire of some patients with LE. Some authors claimed that autoantibodies to type VII collagen are seen in BSLE patients whereas some assumed there is a particular association between EBA and SLE. Also, there have been reported cases with concurrent SLE and EBA, EBA followed by SLE, and SLE followed by EBA [35–39]. Some patients with SLE were reported that had autoantibodies to type VII collagen documented by indirect immunofluorescence (IIF) on split skin, immunoblotting, and immunoelectron microscopy (IEM) methods but no blistering disease [30].

There is a defined genetic base originating from variations in multiple loci in all types of CLEs. While this genetic base leads to susceptibility, exogenous, or endogenous triggers cause the presentation of the disease. The best known trigger is ultraviolet radiation [8, 12–15]. BSLE is associated with an increased prevalence of the HLA class II DR2 haplotype like SLE. This HLA-DR2 haplotype has been found associated with hyperimmunity [40]. Furthermore, antibodies to type VII collagen in BSLE have also been found to be related to the antigen-presenting protein encoded by the DR2-associated DRB1*1501 allele. In other words, this allele was found only in BSLE patients [16]. It is possible that this genetic predisposition is responsible for an increased risk for development of autoimmunity to BMZ antigens. Overproduction of autoantibodies by hyper-reactive B cells as a result of depressed T suppressor activity is an important feature of SLE [8].

In the patients with BSLE, all types of immunoglobulins can be present in the deposits around the DEJ, but the main identified type is IgG, followed by IgA and IgM [22–25]. Ig deposits may be found in biopsies of both lesional and perilesional skin, whereas complement is seen

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in particular in perilesional region. Therefore, it is estimated that antibody-mediated activation of complement may lead to blister formation in BSLE patients [31]. Furthermore, *in vitro* studies have revealed that antibodies to type VII collagen lead to the activation of both complement and neutrophils causing the separation within the DEJ [9, 41, 42]. This proteolysis by leukocytes (induced by antibodies) was previously shown to occur in EBA disease, too [42]. Therefore, the immunopathological similarities and clinical presentations may cause diagnostic confusion between BSLE and EBA. Besides that, a distinct immunological divergence could be shown by the determination of IgG subclass concentrations between EBA and BSLE. IgG2 and IgG3 deposits are found more often in BSLE patients, whereas IgG1 and IgG4 deposits are observed in EBA patients. Even if the functional properties of IgG subclasses are well known, the specific contribution of each subclass to the pathogenesis in autoimmunity to type VII collagen is controversial [8, 22, 31, 41]. The determination of quantity and quality of circulating autoantibodies in the serum of patients is important for diagnosis, prognosis and treatment choices in autoimmune blistering dermatoses [31].

Recke et al. reported that recombinant anti-type VII collagen IgG3 antibody and, a lesser extent, IgG1 autoantibodies, were able to activate complement at the DEJ. IgG2 and IgG4 antibodies were found inactive [31].

1.4. Clinical features

Clinically, BSLE is characterized by rapid onset, tense vesicles, and bullae on the erythematous edematous plaques or normal skin and involves both sun-exposed and nonexposed areas in patients who meet the ACR revised criteria for SLE [2, 5, 7]. Bullae are usually multiple and may resemble bullae of BP, or may be small and grouped like DH lesions [1]. The lesions rapidly expand and have a predilection for face, vermillion border, upper trunk, supraclavicular region, and proximal extremities. Previously, it was thought that BSLE is seen only in sun-exposed areas, but now it has been shown that it can also affect any area of the body including the oral, pharyngeal, nasal, and vulvar mucous membranes [1, 2]. In addition, usually herpetiform vesicles are seen if there is facial involvement in BSLE. These lesions can be on malar areas with erythema and/or, perioral region, and vermilion border. Moreover, there have been some BSLE cases reported that present with only facial lesions as well [43, 44].

Other than vesicles or blisters, erythematous plaques with annular configuration, urticarial eruptions, erosions, crusted lesions and targetoid lesions can also be seen [5, 9]. But interestingly, the primary lesions of chronic discoid, subacute, and acute LE are not commonly seen in BSLE [30]. Pruritus or burning sensation may or may not be present [8, 45]. If there is, pruritus is mild. In contrast to DH, lesions are less often seen on extensor surfaces, however some BSLE cases involving extensors such as hands, knees, or feet have been reported [46, 47].

There are many case reports showing that BSLE can be the initial presentation of SLE in both adults and children [11, 12, 21, 48–51]. Moreover, some authors estimated that BSLE may be associated with increased activity of SLE such as renal involvement, serositis such as pericarditis or pleuritis, pulmonary hemorrhage, cutaneous vasculitis, etc. [11, 12, 17, 21, 25, 44]. Nevertheless, the exact underlying mechanism of developing nephritis in BSLE is not clear. It is estimated that glomerular and/or tubular scarring causes injury to renal extracellular

matrix and by this injury, new expression of collagens, which does not locate in normal glomeruli, is oversynthesized and these antigens can trigger autoimmune reactions [2, 44, 52, 53]. Diagnosis of BSLE is important since BSLE may indicate development of lupus nephritis and resistance to treatment [12, 15, 44].

Most of the patients with BSLE have positive ANA tests. Moreover, anti-dsDNA, anti-Sm, anti-La/SS-B, anti-Ro/SS-A, and anticardiolipin antibodies may also be detected as well. Other laboratory findings that are related to SLE such as elevated erythrocyte sedimentation rate, hypocomplementemia, hematologic abnormalities (anemia, thrombocytopenia, leukopenia), and abnormal urinalysis (proteinuria or/and urine casts) can also be observed in BSLE [16].

1.5. Histopathology

Typically, histopathologic examination of early BSLE lesion shows inflammation and dermoepidermal separation at the BMZ. The epidermis is often intact. In the upper dermis, edema, and dermal papillary, neutrophilic microabscesses are seen similar to histopathological features of DH [1, 8, 25, 30]. In most of the cases, neutrophils are not only seen in the papillae, but also form a continuous linear pattern which is concentrated in the upper dermis, in the blister cavity, and beneath and on the BMZ [30].

A subepidermal blistering and perivascular (around mid and upper dermal blood vessels) inflammatory infiltrate, including particularly lymphocytes, occasionally eosinophils and monocytes, are other histologic features of BSLE. Moreover, in some cases of leukocytoclasis, erythrocyte extravasation and necrosis of blood vessels, which belong to necrotizing vasculitis, may be seen. But in these cases, which have vasculitis characteristics, clinical features of vasculitis do not exist interestingly. Additionally, dermal vasculitis can be seen more frequently in BSLE than DH [8, 17].

Some characteristic histopathological features of LE such as basal layer vacuolization, epidermal atrophy and thickening of the BMZ, mononuclear cell-predominant inflammation, mucin deposition in the reticular dermis are usually absent or rarely found in BSLE lesions [8, 17, 30].

1.6. Direct and indirect immunofluorescence techniques and immunoelectron microscopy

Classic immunopathologic features of BSLE by DIF examination are immune deposits in the upper dermis and along the BMZ and occasionally in upper dermal venules [8, 15, 30, 50]. These deposits include main Igs (IgG, IgA, and IgM), and complements. Complement proteins are usually present in lesional skin but may be absent in clinically normal skin.

Among the aforementioned Ig types, IgG is most commonly seen, while IgM and IgA are present in approximately 70% of cases. These depositions of Igs have two major patterns: granular in approximately 60% of cases and linear in 40%. In a few cases, fibrillar or thready patterns of depositions have been reported as well [8, 15, 53]. Furthermore, in some cases, a mixed pattern with a linear band of deposits and scattered granular deposits has been shown. In this linear pattern, deposits may be bandlike, thin, or widen. Regardless of the pattern of deposition, clinical and histopathologic features of BSLE does not differ, and they are steady [53].

DIF study of BSLE lesions presents a resemblance of EBA; however, they are different from DH. Granular IgA deposits in DH disease are seen as confined to dermal papillae typically; however, in BSLE, it is not seen. Moreover, IgA deposits appear to be more common in BSLE than in SLE patients without blisters [4, 14, 27, 30, 45]. It should be kept in mind that DIF studies of BSLE can be similar to that of CLEs [17, 35].

The substrate used in IIF studies is normal human skin, and it is processed with patient serum to detect the circulating antibodies. In most cases of BSLE, autoantibodies to type VII collagen is detected by IIF studies; however, in some cases, negative staining may be seen, particularly in the patients with granular Ig deposition pattern by DIF. DIF studies on salt-split skin from patients commonly show deposition along the dermal side, some beneath of the lamina densa, and some shows no deposition [36]. This heterogenicity of BSLE cases does not affect the clinical features in patients [53].

IEM shows deposits of Igs as a linear continuous band along the DEJ of dense granular reaction products in the upper dermis beneath the basal lamina. Depositions may also be seen on the lamina densa and in the perivascular region and occasionally in the deeper dermis as well. The deposits do not localize in the lamina lucida, and thus, the possibility of a primary bullous disease such as BP is excluded; because in BP, antibodies are against hemidesmosomal and/or lamina lucida antigens [1, 8].

1.7. ELISA and immunoblotting

Antibodies against 290- and 145-kDa autoantigens (type VII collagen) [36], can be extracted from the sera of BSLE patients via immunoblotting [28]. As mentioned previously, these autoantigens that are seen in BSLE patients are also target antigens in EBA.

Most recently developed method is ELISA, and the diagnosis of BSLE can be made faster and more accurate via ELISA. In ELISA method, NC1 and NC2 domain epitopes of type VII collagen are used to find the presence of circulating antibodies in sera of patients. By this method, differential diagnosis between BSLE and EBA can be provided easily for the reason of EBA patients to have higher levels of IgG1 and IgG4, while BSLE patients have higher levels of IgG2 and IgG3 in their serum [23, 31, 37].

1.8. Diagnosis

The diagnostic criteria of BSLE was first proposed in 1983 [45] and was revised after the administration of salt split-skin immunofluorescence in 1988 [54]. These criteria include:

1. a diagnosis of SLE based on ACR criteria;
2. a nonscarring vesiculobullous eruption;
3. histopathologic features similar to DH-neutrophil-rich infiltrated subepidermal blisters in papillary dermis;
4. positive DIF of perilesional skin with deposition of IgG and/or IgM and IgA at the BMZ,
5. negative or positive IIF testing for circulating autoantibodies against the BMZ via the salt-split skin technique;

The BSLE patients were divided into three groups (**Table 1**) [15, 30] based on the presence of antibodies to type VII collagen and location of the antibodies against the BMZ [25, 30]. Distinguishing subtypes of BSLE based on clinical features is not possible, but could be performed only through immunohistochemistry. Type I patients have circulating or deposited autoantibodies to type VII collagen, as determined by IIF or IEM and type I patients also have been fulfilling all criteria of ACR. However, type II patients do not demonstrate autoantibodies to type VII collagen; they have autoantibodies against undetermined location of antigen or dermal antigen other than type VII collagen, and furthermore, these type II patients satisfy only one to four criteria of ACR [2, 30]. And, autoantibodies to type VII collagen can be shown bound to either epidermal or both dermal and epidermal in type III patients [30, 49].

Type I	
Clinic	Fulfilling all criteria of SLE of ACR; subepidermal, transient, tense vesiculobullous eruption located on any area of the body
Histopathology	Infiltration of neutrophils in the upper dermis, dermal edema, subepidermal blister
DIF	IgG, IgA, and IgM, complement at the BMZ
IIF	Circulating autoantibodies to type VII collagen (+), positive or negative for dermal staining of salt-split skin
ELISA/immunoblotting	Positive or negative reaction to 290 and 145 kDa proteins from human skin basement membrane extracts
IEM	Ig deposits in upper dermis and beneath and on the lamina densa
Type II	
Clinic	Fulfilling one to four criteria of ACR; same as type I
Histopathology	Same as type I
DIF	Same as type I
IIF	Circulating autoantibodies to type VII collagen (−), negative for staining of split skin
ELISA/immunoblotting	Negative reaction to the 290 and 145 kDa proteins from basement membrane extracts
IEM	Scattered granular deposits in the upper dermis, but none on or beneath the lamina densa
Type III	
Clinic	Same as type I
Histopathology	Same as type I
DIF	Same as type I
IIF	Circulating autoantibodies to type VII collagen (+/−), positive for epidermal staining of salt-split skin
ELISA/immunoblotting	Positive or negative reaction to 290 and 145 kDa proteins from basement membrane extracts
IEM	Ig deposits in the epidermis, sometimes in the upper dermis and lamina densa

Table 1. Subtypes of bullous SLE.

Because of similar features between BSLE and other immunobullous dermatoses, the correct diagnosis of BSLE could be done by sum of the clinical, histological, immunohistological, and IEM features and meeting the ACR criteria for SLE [8]. The criteria proposed by Camisa and Sharma were formed before IEM, ELISA, and immunoblotting techniques [54]. These methods which can detect circulating antibodies in serum provide more accurate diagnosis of BSLE [15, 55].

1.9. Differential diagnosis

As mentioned previously, blisters can be seen in all types of CLE including acute, subacute, and chronic CLE. But, these bullous lesions are different from BSLE in terms of their clinical, histological, and pathogenetical features. In all types of CLEs, a genetic base originated from variations in multiple loci leads to susceptibility to LE and disease activity is provoked by exogenous or endogenous triggers. However, in the pathogenesis of BSLE, these genetic susceptibility or triggering factors have not been mentioned clearly [8, 12, 14]. Blisters in CLEs are polycyclic erosions with an advancing blistering border and always seen over an erythematous base predominantly on sun-exposed parts of body. Subepidermal blister formation in CLEs is caused by extensive interface inflammation and basal layer vacuolization which can be seen in CLE [3]. Histologic findings of CLEs such as epidermal atrophy, hydropic changes, apoptotic keratinocytes, and mucin deposits are not expected in BSLE. DIF study in CLEs and BSLE may be similar, while IIF shows different findings [3, 14]. Thus, differentiation of BSLE from other types of CLEs can be done based on clinical features, histopathology, and immunohistochemical examinations [12, 15].

Lesions can mimic other vesiculobullous disease such as EBA, BP, DH and LABD [15]. There are two main clinical presentations of EBA: the classical (mechanobullous, non-inflammatory) and the inflammatory subtypes. In classic type of EBA, skin lesions appear over non-inflamed skin. It also has chronic course with skin fragility, usually resistant to therapy, and often causes to debilitating sequelae. The lesions heal with scarring and milia limited to the trauma-prone skin surfaces [15, 56, 57]. However, lesions of inflammatory type of EBA present with transient tense bullae over inflamed skin like BSLE lesions. The similarity of clinical features between inflammatory type and BSLE can cause confusion in diagnosis, especially in patients with no known prior history of SLE. But there are some clues to differentiate; for instance, EBA is more common in the fourth and fifth decades of life and has usually older patients than patients with BSLE [31]. Clinically, in contrary to lesions of EBA which sometimes presents with fragile blisters appearing over hands, knuckles, elbows, knees, and sacrum like dystrophic type, lesions of BSLE are nonscarring, and milia or fragility of the skin on trauma-exposed areas are not expected characteristics [10, 57]. Furthermore, hypo- or hyperpigmentation may remain after healing as well [8]. Also, there is another subset of patients with predominant mucous membrane involvement, and indistinguishable from cicatricial pemphigoid (CP) clinically, presenting with blisters and scarring in the oral, ocular, vaginal, and other mucous membranes, leading to significant dysfunction of organs, and even death [7]. The histopathology of EBA is quite heterogeneous but has much less dermal inflammatory infiltrate in classic type of EBA in comparison to BSLE [8]. Immunopathological similarities and diagnostic challenge that exists between BSLE and EBA can be also surmountable by

IgG subclass concentration analysis. As mentioned previously, IgG2 and IgG3 deposits are more in BSLE patients, while IgG1 and IgG4 deposits are more often in EBA patients [8, 22, 31, 41]. In addition, EBA has been related to many systemic diseases including hematologic, infectious, and endocrine conditions, autoimmune disorders, malignancies, and particularly inflammatory bowel diseases (IBD) [58]. EBA is a chronic autoimmune disease, oral mucosal involvement may be extensive, and more resistant to treatment with steroids, dapsone, and other immunomodulatory agents, whereas lesions of BSLE can recover completely with treatment [56]. Also, occasionally some BSLE cases were reported with features of EBA [39, 59].

BP is one of the main diseases in the differential diagnosis of BSLE. BP is characterized by tense bullae, erosions, and crusts that arise on normal or erythematous skin on the entire body but mostly trunk, extremities. Bullae usually heal without scarring or milia formation and patients mostly have pruritus that may precede blistering by months [60]. BP is more common in elderly patients, especially over 65 years old [10]. Histopathological findings are subepidermal blisters with inflammatory cell infiltrate in the superficial dermis containing predominantly eosinophils. Neutrophilic microabscess does not exist contrast to BSLE [10]. It is thought that eosinophils have an important role in blister formation via degranulation at the BMZ. Early prebullous, urticarial-type lesions may show eosinophilic spongiosis as well. About 70% of BP patients have elevated serum IgE and about 50% have blood eosinophilia. DIF study of perilesional skin shows linear deposits of complement C3 (90–100% of patients) and IgG (70–90% of patients) at the BMZ. It is important to know that if DIF is negative for C3, the diagnosis of BP is suspicious [61]. IIF study shows circulating IgG that binds the epidermal basement membrane in most cases. ELISA test for BP180 and BP230 antibodies is positive. The negative pemphigoid serologies by ELISA tests, incompatible histologic and IF findings help to differentiate BSLE from BP [8].

In patients with LE, all blistering eruptions may not be BSLE all the time. Additionally, these patients tend to have co-morbidities which need many medications that can lead to bullous drug reactions. Also, sometimes patients with a severe acute or subacute CLE may resemble the symptoms of erythema multiforme (Rowell syndrome) or toxic epidermal necrolysis (TEN). In these type of patients, the eruptions are expected to develop rapidly or evolve over several weeks. And also in TEN-like acute CLE, lesions start as diffuse or patchy erythema, more often on sun-exposed part of body and later, and evolve into flaccid annular bullae rapidly. They also show positive Nikolsky sign, whereas in BSLE nikolsky sign is generally negative. Histopathology of these lesions show solitary necrotic keratinocytes at lower epidermis, junctional vacuolar degeneration, intensive periadnexal and perivascular lymphocytic infiltrates, thickened BMZ, the presence of plasma cells or mucin unlike TEN and BSLE [62, 63]. Furthermore, DIF examination of this LE lesions sometimes shows granular deposits of IgG and/or IgM, and less commonly IgA, at DEJ; but this could not be seen all the time, meanly a negative DIF does not rule the LE out [64].

In these patients with TEN-like CLE, often severe systemic disease involvements are seen such as lupus nephritis, or cerebritis, etc. The underlying mechanism of TEN-like CLE may be related to Fas-Fas ligand interactions, which have resulted in the massive keratinocyte apoptosis. This severe condition of CLE, mostly have to be treated with IVIG and/or systemic corticosteroids [16].

Moreover, there have been other primary blistering disorders reported in association with LE, including pemphigus vulgaris, LABD, porphyria cutanea tarda, fixed drug eruption (FDE),

Stevens-Johnson syndrome (SJS), TEN as well. FDE lesions are characterized by sharply marginated, round- or oval-shaped lesions that can have central bullae [8]. These bullae may be seen widespread like TEN. To differentiate FDE from other bullous presentations, some clues are important to know. In FDE, a drug history must be exist like SJS/TEN but, in FDE patients recurrent episodes are typically seen in minutes to hours after re-exposure to a particular medication, whereas in SJS/TEN, recurrent episodes due to the medication can occur in as early as 2 days. FDE lesions occur in the same location as previous episode. Histopathological findings of FDE lesions show superficial and deep perivascular mixed infiltrate with lymphocytes, neutrophils, eosinophils, and histiocytes. However, in TEN, typically there is usually only a superficial perivascular infiltrate with lymphocytes and histiocytes. DIF of FDE lesions is not well described; linear IgG and C3 deposition along the BMZ, perivascular, and intercellular IgG and C3 were reported. Thus, in addition to history, clinical feature, and histopathology, DIF method helps to rule out FDE from BSLE [64].

In SJS/TEN, which have a significant mortality risk, there can be extensive skin involvement with especially annular lesions and moderate-severe mucosal involvement with a clear drug association. However, in BSLE generalized skin involvement is rarely seen and mucosal involvement is uncommon. Also, in BSLE there has been no known drug association either. Prognosis is poor in SJS/TEN; in BSLE prognosis depends on the systemic components of SLE [24, 25, 65]. But differentiation from these diseases depends primarily on history, clinical features, histologic findings, and DIF tests [66–68].

As mentioned previously, DH is also involved in the differential diagnosis of BSLE. DH, also known as Duhring's disease, is a chronic autoimmune bullous disease, associated with celiac disease and gluten sensitivity. It is claimed that DH can be regarded as a skin manifestation of gluten sensitivity, a systemic disorder capable of affecting multiple organs. [69]. DH is characterized by grouped erythematous excoriated papules or plaques with small, clustered herpetiform vesicles, and tense blisters distributed symmetrically over extensor surfaces—particularly elbows, knees, buttocks, and shoulders, rarely on the oral mucosa. The eruption of DH most often begins between the ages of 15 and 50 years and persists indefinitely. Patients have generally intense itching and burning sensation [70]. There is an association with the genotypes HLA DR3, HLA DQw2, found in 80–90% of cases. HLA-Al, -B8 are also found to be as related genotypes. Celiac disease has association with HLA-B8, HLA-DR3, and HLA-DQw2 histocompatibility complex antigens as well. This means DH and celiac disease have a common immunogenetic background [71]. Morbidity is mainly related to the intense pruritus, scratching, discomfort, commonly seen superimposed infections. Also, systemic complications are related to the associated gluten-sensitive enteropathy. Celiac disease is accepted to be present in all patients with DH, but some of these patients have subclinical gastrointestinal disease with no symptoms, only histological findings as well. Gastrointestinal symptoms of patients with DH are milder than those seen in patients with celiac disease without skin lesions [72]. Histopathologic examination of the lesion shows subepithelial bulla with neutrophils in the dermal papillae, fibrin deposition, and edema. Usually, papillary neutrophilic microabscesses progress to subepidermal vacuolization and vesicle formation. In DIF microscopy granular IgA deposits in dermal papillae of perilesional skin is found [48]. The clinical and histopathological features of DH can be the same as those of BSLE. Extensor surface involvement is less common in BSLE and pruritus is usually absent or mild [8]. Contrary to

BSLE, in DH the markers of gluten sensitivity: anti-gliadin, anti-endomysium, and anti-tissue transglutaminase antibodies are important characteristics, and gluten-free diet, dapsone, and sulfone therapy are the main choices of treatment. In BSLE, IgG and IgM can be found in addition to IgA in the BMZ. Thus, this finding helps to differentiate BSLE from DH, in which only IgA deposits are observed [48].

LABD is an autoimmune mucocutaneous disorder that characterized by subepithelial bullae caused by IgA autoantibodies. These autoantibodies are directed against BMZ and the genetic basis of the disease is found related to HLA Cw7. Although it was previously confused with DH; now they are well-recognized distinct entities. Furthermore, in contrast to DH, there is no association with gluten-sensitive enteropathy, and the gluten-free diet is ineffective in LABD disease as well [73]. Bullae may be clear or hemorrhagic, tense like BP bullae, vary in size, and frequently tend to form annular or polycyclic plaques and they have risen out of normal skin, or on an erythematous or urticarial base. LABD can be seen at any age, but there are two peaks of onset: at 40–60 years of age and in children of preschool age. It has a heterogeneous clinic based on age of onset, clinical features, and distribution. In children, vesiculobullous lesions are mainly seen on the lower abdomen and the perineal area, whereas face, hands, and feet are rarely involved. Blisters commonly occur in a "cluster of jewels" pattern [74]. However, in adults, LABD lesions mainly involve extensor surfaces, buttocks, trunk, and the perioral area. These lesions are usually highly itchy. All mucous membranes may be involved; particularly, the oral cavity and eyes are the most common affected mucosal area. Lesions of the oral cavity cause generally severe pain. LABD may be idiopathic or associated with SLE [75], inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis [76], infections [77], malignancies-particularly hematologic cancers [78], and drugs such as vancomycin, captopril, acetaminophen, and phenytoin [79]. Physical trauma and ultraviolet exposure have been also reported as triggering factors in the pathogenesis of LABD [80]; however, in the literature, most cases of LABD are idiopathic [7].

The histopathologic examinations of LABD lesions show a subepithelial blister with a predominant neutrophilic infiltrate—occasionally eosinophils and mononuclear cells—in the upper epidermis that forms papillary microabscesses. The DIF examination of LABD shows the presence of IgA deposits along the BMZ in a linear pattern. IIF generally shows a variable positivity of 30–50% of circulating IgA autoantibodies in LABD patients [81]. Usually, dramatic response to sulfones or sulfonamide is seen in LABD patients. In idiopathic cases of LABD, dapsone treatment is the best choice [82]. Based on clinical and histologic features alone, it may be hard to distinguish LABD from BSLE. Therefore, one or more advanced methods such as DIF, IIF, salt-split skin, Western immunoblotting, and IEM should be used to differentiate these diseases [83].

1.10. Treatment

For other cutaneous manifestations of SLE disease, the main treatments are topical and systemic steroids and antimalarials [5]. Differently from these cutaneous lesions, BSLE lesions are often recalcitrant to the high dose systemic corticosteroids which are used to treat the other systemic manifestations of SLE [1]. The primary treatment choice in BSLE is dapsone and this is one of distinguishing features of BSLE from most of other autoimmune bullous dermatoses. Even with low doses (25–50 mg/day) of dapsone, improvement of skin lesions is expected to be observed within the first 24–48 h of the therapy. However, during dapsone

therapy, improvement in the systemic involvement often does not parallel the cutaneous response. For example, Kettler et al. [84] reported a child case of BSLE whose cutaneous eruptions responded rapidly to the treatment of dapsone, whereas the oral ulcers did not improve without prednisone therapy. Beside this, they used prednisone treatment alone, but cutaneous eruption of the patient did not improve either. Oral ulcers healed after starting the combination therapy of dapsone, prednisone, and sulfapyridine. As distinct from most of BSLE cases, Alarcón et al. reported a case of BSLE whose rashes worsened by dapsone treatment. The patient was recovered by systemic steroid therapy [85].

Total regression of cutaneous lesions is generally seen within weeks [1, 8, 27, 37, 86]. Dapsone has several mechanisms that mainly act via interference with the chemotaxis-adherence-cytotoxic enzymes of neutrophils [87].

The main adverse effects of dapsone treatment are methemoglobinemia, hepatitis, headache, motor neuropathy, exfoliative dermatitis, and fatal agranulocytosis. Especially patients with glucose-6-phosphate dehydrogenase deficiency may present with severe hemolysis after dapsone treatment. Therefore, patients should be tested for this enzyme deficiency before being treated with dapsone. Furthermore, in BSLE patients, the risk of hemolysis is higher than DH patients. So, it is recommended that the dapsone dosage per day should not exceed 1.5 mg/kg to minimize this side effect [21, 87]. Interestingly, it has been reported that in some cases with BSLE, dapsone treatment lead to exacerbation of lesions [5, 85].

Dapsone can be stopped by tapering, but there is no exact time to stop the treatment and usually there has been no relapse reported in BSLE patients [8, 88]. Recurrences are often seen rapid after the withdrawal of dapsone. However, restarting the treatment can provide prompt remission [88]. In general, discontinuance of dapsone therapy is usually recommended after 1 year.

Furthermore, sometimes—especially if systemic involvement is significant such as nephritis—dapsone is not sufficient. Steroid treatments or other immunomodulatory treatments such as azathioprine, methotrexate, cyclophosphamide, antimalarial agents, and MMF can be used for these patients or for the patients who fail to respond to dapsone or have intolerance to dapsone [4, 5]. In addition, rituximab was recently reported to be effective in cases of BSLE with no response to dapsone and other immunomodulatory treatments [15, 18, 89]. Anyanwu et al. reported an oral BSLE case treated successfully with rituximab [90].

Moreover, Pehr [91] reported that in the youngest case of BSLE, the combination of MMF and erythromycin was found to be effective. Interestingly, in that case, neither dapsone nor medium- to high-dose systemic steroid treatments provided benefit. Near-perfect control of BSLE was provided in some cases after combination therapy of erythromycin and MMF was administered. MMF had been used in other bullous diseases of children with good results and for systemic manifestations of childhood LE [92–94]. MMF acts via blocking de novo purine synthesis, thereby interfering with lymphocyte proliferation. Although erythromycin is an antibiotic, it also probably acts as an anti-inflammatory agent via interference with matrix metalloproteinase 9. Thus, MMF used in combination with erythromycin is thought to have synergistic effect. Furthermore, in the previous cases of bullous LE in childhood, following treatments were used: systemic steroids, dapsone, azathioprine, cyclophosphamide, sulfapyridine, and hydroxychloroquine [91, 95, 96].

Also, there have been some reported BSLE cases that were successfully treated with IVIG therapy [13, 97, 98].

If the treatment of BSLE is summarized, after diagnosis of BSLE was made based on criteria first of all, it should be asked whether systemic complications of SLE are present or not. If answer is no, then dapsone treatment can be first choice drug with or without immunosuppressants. If answer is yes, a systemic complication is present; then corticosteroids, azathioprine, cyclophosphamide, antimalarials, methotrexate, MMF and rituximab, IVIG may be the drug choices and they could be applied alone or in combination [15].

1.11. Prognosis

Treatment with dapsone is successful in most cases of BSLE [5]. Frequently, lesions resolve spontaneously in less than 1 year and, to prevent recurrences, discontinuance of dapsone therapy is usually recommended after 1 year [88]. In some BSLE cases with severe systemic manifestations of SLE, prognosis is similar to systemic SLE. But, the development of BSLE in patients with SLE does not cause to increased mortality. In these patients, immunosuppressants and immunomodulatory drugs are preferred rather than dapsone [5, 6].

2. Cicatricial pemphigoid

2.1. Introduction

Cicatricial pemphigoid, (synonyms: mucous membrane pemphigoid, oral pemphigoid, desquamative gingivitis, ocular cicatricial pemphigoid) is an inflammatory disorder characterized by subepidermal blisters. CP affects particularly mucous membranes but cutaneous involvement can also be seen in some cases [99, 100]. The lesions usually heal with scarring, and CP may cause fatal outcomes such as airway obstruction. So, clinicians should recognize this rare entity as immediate as possible to prevent its complications [99]. CP patients must be evaluated by multidisciplinary team approach which involves primary care physicians, dentists, ophthalmologists, dermatologists, gynecologists, gastroenterologists, and otolaryngologists [100].

2.2. Epidemiology

CP is the second most frequent subepidermal blistering disease. It usually affects the older population (60–80 years of age), and children are rarely encountered as well. CP is seen approximately 1.5–2 times more in women than men [101]. There are about 20 cases of childhood onset CP reported, of which the youngest is 10 months old [102–104]. There is no known racial or geographic predilection [105].

The actual incidence of CP is unknown, however it was found as about 1.3–2.0/million/year in France and also a prevalence of 24.6/million in 2014 was reported in Germany [106, 107]. For ocular pemphigoid—a CP type with conjunctival involvement exclusively—an incidence of one new case/million/year was reported in England as well [108, 109].

2.3. Etiopathogenesis

The etiopathogenesis is still unknown; however, it is thought that environmental factors combined with genetic susceptibility lead to CP. There have been some reported cases of CP triggered by human immunodeficiency virus, diphtheria vaccination, and some medications such as methyldopa, clonidine, and D-penicillamine [110, 111]. In addition, other autoimmune diseases may occur more frequently in patients with CP [112]. Moreover, some bullous diseases may indicate the presence of an underlying malignancy. Especially, lymphomas and epithelial malignancies should be ruled out in autoimmune bullous diseases as well as MMP [113]. A possible association with HLA haplotypes (HLADQB1* 0301) and HLA-4 have been described in CP patients [105, 114]. It is suggested that a genotype of the interleukin (IL) 4 receptor A-1902 A/A, which is found in 90% of patients with oral pemphigoid, reduces the response to IL-4 and this may be connected with low risk of scarring in oral involvement [115].

Production of autoantibodies responsible for the disease is initiated by the loss of immunologic tolerance against the components of the basal membrane. A variety of different autoantigens including BP antigen (Ag) 230 (BPAg1, a 230-kDa protein, BP1), the BPAg180 (a 180-kDa protein, BP2), Lam-332 (also called epiligrin), integrin α6, integrin β4, the 97/120-kDa LABD antigen, type VII collagen, and some antigens such as a 45-kDa protein, uncein, a 168-kDa epithelial protein, and a 120-kDa epithelial protein have been described in patients with CP. The two major autoantigens of CP are BPAg2 and Lam-332. BPAg1 and BPAg2 are components of hemidesmosome structure. BPAg1 is an intracellular protein implicated in the organization of the keratin filament network; whereas, BPAg2 and integrin α6-β4 are transmembrane proteins that contribute to the assembly and stabilization of hemidesmosomes. Autoantibodies predominantly identify the C-terminal epitopes of BP180, but, NC16A is the second immunodominant domain. Lam-332 establishes connection between anchoring ligaments and transmembrane proteins. It is a heterotrimeric glycoprotein situated on the BMZ, including α3, β3, and γ2 subunits. Most of CP patients with anti-Lam-332 antibodies were reported to have autoantibodies to the α3 and γ2 subunits, and less frequently to the β3 subunit of the Lam-332 [99, 116–118].

Complement is activated by antigen antibody ligation and the cytokine/chemokine release leads lysis of cell membrane, infiltration, and degranulation of effector cells that cause clinical inflammation and tissue destruction. Thereafter, aggregation of inflammatory cells induces subsequent activation of fibroblasts. Fibroblasts multiply and secrete collagen, and by this action, subepithelial fibrosis has been started. Cytokines, particularly transforming growth factor beta (TGF-β), IL-13, tumor necrosis factor (TNF-α) may play a significant role in the pathogenesis of conjunctival scar tissue formation in CP patients [119, 120].

2.4. Clinical features

The oral mucosa is the most affected part of the body, ocular, nasal, nasopharyngeal, anogenital, laryngeal, esophageal mucosa, and skin can be involved. If there is cutaneous involvement, mostly skin of head and upper body are affected. More than one mucosal region may be simultaneously affected. In CP cases with predominantly mucosal involvement, scarring is more often. CP lesions are recalcitrant to treatment and this is a distinctive feature of CP from

other bullous diseases. Although scarring is an important clinical feature of CP, it may not be present in areas such as the oral mucosa. Complications such as blindness, airway obstruction are observed on the areas where the disease leads to scar formation [99, 121].

The distribution of disease may be local or widespread. The severity of the disease is associated with the magnitude of effected area. Localized lesions may progress to the extensive disease. The patients with only oral mucosa and/or skin involvement have less risk for scarring and this group is defined as "low-risk" CP patients. On the contrary, "high-risk" patients have lesions in any of the following sites: ocular, nasopharyngeal, esophageal, laryngeal, and genital mucosa [99, 122, 123].

Murrell and colleagues have established the Mucous Membrane Pemphigoid Disease Area Index for use in clinical studies for intervention and evaluation of CP patients (**Table 2**) [124].

Oral mucosa is the most frequently involved and is often the first (or sometimes solely) affected region in patients with CP. Desquamative gingivitis is generally the first finding of oral CP. Painful, erosive/blistering lesions occur often in the gingival, buccal mucosa, and palatal region. Tongue, lips, and alveolar ridge are rarely affected. The lesions can frequently recur at the same region. Erosions, desquamative gingivitis are observed in the acute period of the oral disease, whereas complications such as delicate pattern of reticulate scarring, periodontal ligament damage, loss of bone mass, teeth loss, or adhesions are noted during the chronic period [121].

Ocular involvement is also seen commonly in patients with CP. Isolated ocular involvement is present in some patients. Generally, the mean age of onset is 65 in this clinical subtype, but it is more aggressive in younger patients. Ocular findings may be nonspecific in the early stages of the disease (such as burning, dryness, photophobia, or foreign body sensation). Blisters are rarely observed. The ocular involvement is usually unilateral at the beginning, but the opposite eye is also involved in following years. Ocular CP may result in development of symblepharon, ankyloblepharon, entropion, trichiasis, corneal ulceration, neovascularization, and blindness. Ocular CP should be evaluated by an experienced ophthalmologist and distinguished from other ophthalmologic diseases. Slit-lamp examx may be useful for early diagnosis of ocular CP [99, 125].

Genital involvement in males generally results in erosions on the glans, urethral strictures, and phimosis [126]. Interestingly, female patients may be asymptomatic. But erosions on the labia minora/majora, dysuria, vaginal discomfort, dyspareunia may be present and consequently fusion of the labias may be seen [127].

Nasopharyngeal involvement is another clinical output of CP and findings such as epistaxis, dysphagia, dysphonia, nasal obstruction, and nasal crusting can be seen [128]. Laryngeal involvement may cause fatal airway obstruction requiring tracheostomy [125]. There is esophageal involvement in approximately 2–7% of patients that may cause dysphagia, odynophagia, aspiration, strictures, and malnutrition as well [129].

Skin involvement is detected in 25–35% of CP patients. Clinical presentation is frequently small, tense vesicles, or bullae on the scalp, head, neck, and upper trunk. The cutaneous lesions are usually smaller in size and sometimes recur in the same region. Accompanying atrophic scars and milia can be observed in the lesion sites [121].

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Disease activity		Damage	
Erosions-blisters and new erythema in ears, forehead, rest of the face, neck, chest, abdomen, shoulders, buttocks, arms and hands, legs and feet, anal, genital sites	0 = absent; 1 = 1–3 lesions; furthest 1 lesion >2 cm in any diametery, none >6 cm; 2 = 2–3 lesions, at least 2 lesions >2 cm diameter, none >6 cm; 3= >3 lesions, none >6 cm diameter; 5= >3 lesions, and/or at least 1 lesions >6 cm, 6= > 3 lesions, and/or at least 1 lesions >16 cm diameter of entire are	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions-blisters and new erythema in scalp	0 = absent 1 = 1 quadrant 2 = 2 quadrants 3 = 3 quadrants 4 = affects complete scalp 10 = at least 1 lesion >6 cm	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions/blisters in eyes	0 = No erythema 1 = Light pink 2 = Moderate pink 5 = Dark pink 10 = Bright red	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1
Erosions/blisters in other mucosa	0 = absent 1 = 1 lesion 2 = 2–3 lesions 5= > 3 lesions or 2 lesions >2 cm 10 = whole area	Erythema/ postinflammatory hyperpigmentation/ scar	Absent = 0 Present = 1

Table 2. Mucous membrane pemphigoid disease area index [124].

CP is divided into subsets according to antibody profiles and sites of involvement. The disease caused by Lam-332 antibodies is called antiepilegrin CP (AECP). AECP is estimated to comprise of 5–20% patients of CP. The patients in this group are clinically indistinguishable from other forms of cicatricial pemphigoid and some of these patients may occasionally have antibodies directed against Lam-331. Egan et al. demonstrated that 100% of the patients had mucous membrane involvement and 86% had mild to moderate skin involvement in AECP [130, 131].

Some of the patients with CP may have restricted disease with ocular mucosa involvement or may have a clinical course that predominantly not only affects the ocular mucosa, but also involves other mucosal sites. This form of disease is called ocular CP and antibodies to a portion of the intracytoplasmic component of human integrin-β4 and/or BP-180 are detected in

this group of patients [132]. Another variant within the CP phenotype is anti-BP180 MMP, where the patients have circulating IgG antibodies to BP antigens. Both of the skin and mucous membranes are involved in this variant. BP180 C-terminal domain and BP180 NC16a domain are considered to be the major antigenic domains in anti-BP180 MMP [133].

Another subset of CP is called oral pemphigoid, in which the autoantibodies to human alpha-6 integrin subunit are thought to be responsible for the disease. The patients with this type of CP have limited disease to the oral mucosa with no skin or other mucosal involvement [134, 135].

CP is rarely seen in children and it is called childhood CP. Ocular and genital mucosa involvement is common in children. Linear IgA deposits was detected and reported like LABD. In view of the fact that conjunctival scarring can also be seen in patients with LABD, it has been discussed whether CP and LABD should be classified as the same disease or whether they are different entities [136] .

Brunsting-Perry CP is a rare variant of CP characterized by blisters, hemorrhagic crusts, and mainly atrophic scars. The lesions are observed predominantly located on the head, neck, scalp, and upper aspects of the trunk with only mild or no mucosal involvement. There is no specific antigen of Brunsting-Perry CP. This variant is seen in middle-aged or elderly patients, with a male predominance [137, 138]. Some authors have suggested that Brunsting-Perry CP may a clinical variant of EBA [139].

2.5. Diagnosis

Diagnosis of CP is made based on clinical, histological, and immunopathological findings. The diagnosis of CP is often difficult, especially in early stages, because of variations in clinical presentation and on histopathological examination.

Histopathological examination of CP lesions shows subepidermal split (without acantholysis) and dermal leukocytic infiltrations mostly composed of lymphocytes, histiocytes, as well as variable number of neutrophils and eosinophils. The inflammatory infiltrates in mucosal lesions contain plasma cells. Mast cells may be detected in biopsy specimens of the conjunctiva as well. Similar findings can be seen in BP, LABD and EBA. Histopathological examination of older lesions shows fibroblast proliferation and fibrosis [140].

The electron microscopic examination shows epithelian findings including intracellular edema, decreased number of goblet cells, granular materials and fragmentation, duplication, thickening in BMZ. According to Thorne et al., the sensitivity and specificity of electron microscopy in ocular CP were found as 51 and 72%, respectively [141].

IEM studies have shown that the immune deposits are located in lamina lucida, lamina densa, hemidesmosomes, and basal keratinocyte cytoplasm [140].

DIF microscopy characteristically shows a continuous, linear n-serrated pattern of IgG (frequently IgG4), C3, less commonly IgA, IgM, and fibrin or a combination of these along the BMZ. DIF is the gold standard test for diagnosis of CP, but it is also known to have high false negative rates especially in ocular CP. Shimanovich et al. found that DIF staining was positive in 74 of 78 patients (95%); however, multiple and recurrent biopsies were taken from the patients.

The sensitivity of DIF microscopy was increased with multiple and repeated biopsies. [142]. Power et al. claims that using immunohistochemistry which includes immunoperoxidase technique may increase the sensitivity of conjunctival biopsy in the diagnosis of ocular CP [143, 144].

ELISA systems and IIF can be used to determine circulating antibodies. Normal human epithelial substrate (e.g., 1.0 M sodium chloride–split skin) is used in IIF and IIF reveals binding to the roof (epidermal) or floor (dermal) of the blister depending on the antigen targeted. While, patients with integrin and BP180 autoantibodies display circulating IgG autoantibodies that bind to the epidermal side, Lam-332 autoantibodies bind to dermal side of salt-split skin by IIF [99, 140].

According to Amber's study, which included the patients with positive immunoblot or immunoprecipitation to NC16a, ELISA test including both NC16a and C-terminal portion of BP180 demonstrated 73% sensitivity and 93% specificity. But, when they tested IgG reactivity against the C-terminal domain of BP180 in the same patients, both the sensitivity and specificity decreased to 43 and 56%, respectively. The sensitivity of ELISA reached 75% in the patients who have IgG reactivity against the Lam-332-a3 subunit [145]. According to another study, the titer of IgA antibodies to NC16a in saliva was found correlated with sera [144].

Serum autoantibodies against BP230 are more frequently detected when anti-Lam-332 autoantibodies are also present. This association was thought to be possibly related to epitope spreading [107]. Bekou's study showed that 78% of patients with CP had serum anti-Lam-332 autoantibodies. Sensitivity and specificity of the Lam-332 ELISA for CP were 75 and 84.3%, respectively, in the same study [146].

Some authors have also suggested that a dual IgG and IgA serum anti-BMZ antibodies are associated with a more severe disease. Additionally, serum titers of anti-BMZ IgG autoantibody often correlate well with disease severity [147]. LAD-1 is an extracellular C-terminal domain of BP180. Dual IgG and IgA reactivity with BP180 and LAD-1 was found to be associated with severe phenotype [148].

Also, there is another popular technique, BIOCHIP mosaic slides have been found to be useful in screening autoantibodies in autoimmune bullous diseases (AIBD). These consisting of different antigen substrates (monkey esophagus, primate salt-split skin, recombinant BP180 NC16A, membrane-bound Dsg 1 ectodomain, Dsg 3 ectodomain, and the C-terminal globular domain of BP230) allow polyvalent IF tests and provide antibody profiles in a single incubation. Technically, it is a modified-IIF, wherein serum from patients with suspected AIBD is added to these slides and examined under fluorescence microscopy. BIOCHIP technique is a simple, standardized, and readily available technique which is useful to screen autoantibodies in AIBDs as well as to identify the target antigen [149].

2.6. Differential diagnosis

Disorders that should be differentiated from CP include pemphigus, other subepidermal immunobullous disease, erythema multiforme, SJS, lupus erythematosus, lichen planus, lichen sclerosus (especially in the anogenital area), drug-induced hypersensitivity reaction. If there is ocular involvement, other conditions causing fibrosis in the conjunctiva should be considered, such as Sjogren's syndrome, scleroderma, severe chronic infectious conjunctivitis,

burns. Some drugs (e.g., pilocarpine, guanethidine, ephedrine, idoxuridine, epidermal growth-factor receptor tyrosine kinase inhibitors) may cause inflammation and fibrosis in the conjunctiva as well. This is called pseudopemphigoid. These patients are clinically indistinguishable from other autoimmune bullous diseases. Specialized immunopathologic studies and/or IEM may be required for diagnosis [112, 125]. It also has been reported that ocular CP developed after Steven Johnson syndrome and Lyell syndrome in some cases. It is thought that the chronic eye surface damage in these cases may trigger the autoimmune process [150].

2.7. Treatment

The main purpose of CP therapy is to prevent scar development, complications such as blindness and airway obstruction. Treatment should be initiated in the early period to prevent complications. Co-operation of oral medicine experts, dermatologists, ophthalmologists, otolaryngologists, and gastroenterologists is important for treatment. The factors determining the treatment regimen in CP are localization, disease severity, and progression rate. CP patients were divided into two groups according to an international consensus. The first group includes patients with oral mucosa and/or skin involvement (low risk); second group includes ocular, laryngeal, esophageal, or genital involvement (high risk) patients. Topical treatment is an initial choice for low-risk patients. However, a more aggressive treatment plan is proposed for high-risk patients even in early period of disease [99]. For the low-risk patients, an initial treatment of moderate-high potency topical corticosteroid can be tried. Depending on the condition of the patient, dapsone (50–200 mg/day), tetracycline (1–2 g/day)/nicotinamide (2–2.5 g/day), sulphamethoxypyridazine (0.5–1 g/day), sulphapyridine (0.25–1 g/dl) can be administered. In the condition of partial response to treatment or progressive disease, systemic corticosteroids are needed for treatment of the patients with no contraindication. If there is an existing contraindication about systemic corticosteroid, other medications like azathioprine, mycophenolat mofetil, cyclophosphamid can be used. IVIG and/or rituximab are the options if there is no response to other mentioned drugs. The treatment begins with systemic corticosteroid, azathioprine or MMF in patients with severe clinic/high risk. The agents may be changed according to clinical course [151].

High potency topical glucocorticoids (fluocinonide, clobetasol propionate, and betamethasone dipropionate) are the first choice agents. They can be applied as a spray, gel or ointment base. Mouthwash (dexametasone 100 mg/ml, 5 ml per rinse) can be used by shaking and spitting for oral lesions. Oral insertable prosthetic device may facilitate the symptoms for oral mucosa. Intralesional corticosteroid therapy may be used instead of topical corticosteroid. Systemic absorption should be considered during application of topical corticosteroid. Antifungal treatments should be used in cases with secondary candidiasis infection [125, 151]. Patients should be recommended to improve oral hygiene and try to avoid rigid foods. Topical formulations of tacrolimus, cyclosporin, mitomicin C (topical and subconjunctival applications) have been described for advanced treatment of CP [152, 153].

Systemic corticosteroid (prednisolone 0.5–1.5 mg/kg/day) have a rapid onset of action; however, the adverse effects such as hyperglycemia, hypertension, hyperlipidemia, osteoporosis, gastric ulcers, secondary infections, and alterations of mood or even psychosis associated with long-term use limit their value [151, 154].

Dapsone therapy is accepted to be the first line of treatment for mild to moderate ocular CP. Adverse effects include hemolysis, methemoglobinemia, dapsone hypersensitivity syndrome (fever, lymphadenopathy, hepatic damage, and generalized erythematous pustules). Patients should be monitored periodically for these side effects [155].

Biologic agents including etanercept, rituximab, infliximab, and daclizumab can be effective in controlling severe CP cases that are resistant to conventional immunosuppressive agents [156–158]. Lymphoma protocol is used for rituximab therapy, which involves a dose of 375 mg/m^2 administered weekly for four consecutive weeks. In patients treated with rituximab, the clinical response was usually obtained 3–6 months after the first dose [159, 160].

IVIG therapy (1–3 g/kg/cycle) can be used in treatment of CP patients who do not respond to conventional therapy or are unable to use them because of various side effects. For recalcitrant ocular CP, combination therapy of rituximab and IVIG is a potent treatment regimen. The most common side effect is headache, followed by nausea [161, 162]. Plasmapheresis has found to be effective in some recalcitrant patients, as well [163].

Eyelid abnormalities such as trichiasis, distichiasis, entropion, lagophthalmos, and symblepharon stenosis of the upper airway, esophageal, and anogenital stricture may need to be managed surgically. Surgical management aims to achieve temporary symptomatic relief and is not a curative treatment for CP [132].

2.8. Prognosis

CP is typically a chronic and progressive disease. CP rarely undergoes spontaneous remission and relapses are seen commonly. Ocular, nasopharyngeal, esophageal, and laryngeal involvement are related with high risk. Anti-Lam-332 antibodies are associated with severe disease and internal malignant neoplasms including solid tumors and lymphomas. The risk of cancer is highest during the first year of disease [107]. Egan's study demonstrated that the relative risk for cancer was 15.4 in the first year of disease onset. Adenocarcinoma (lung, colon, stomach, endometrial) was frequently detected in this study [131]. In a study, various internal malignancies were found in BP180-CP, but the relationship between BP180-CP and internal malignancy is still unclear [133].

3. Conclusion

BSLE and CP are rare autoimmune bullous disorders that have their own characteristics. But sometimes, BSLE may resemble other autoimmune bullous disorders and CLE associated bullae. Moreover, BSLE may be related to increased systemic disease activity of SLE, especially nephritis. So, diagnosis of BSLE is very important and accurate diagnosis requires a high index of clinical suspicion. Scarring of the lesions in CP causes significant complications such as blindness. Early diagnosis and early treatment have a critical role for preventing the scar development. Systemic adjuvant immunosuppressive therapy is required for patients with progressive disease.

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References

[1] Sebaratnam DF, Murrell DF. Bullous systemic lupus erythematosus. Dermatologic Clinics. 2011 Oct;**29**:649-653. DOI: 10.1016/j.det.2011.06.002

[2] Grover C, Khurana A, Sharma S, Singal A. Bullous systemic lupus erythematosus. Indian Journal of Dermatology. 2013;**58**:492. DOI: 10.4103/0019-5154.119973

[3] Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: Issues in diagnosis and treatment. American Journal of Clinical Dermatology. 2009;**10**:365-381. DOI: 10.2165/11310780-000000000-00000

[4] Yung A, Oakley A. Bullous systemic lupus erythematosus. The Australasian Journal of Dermatology. 2000 Nov;**41**:234-237. Review. DOI: 10.1046/j.1440-0960.2000.00426.x

[5] Fu X, Xu M, Liu J, Qi Y, Li S, Wang H. Regulation of migratory activity of human keratinocytes by topography of multiscale collagen-containing nanofibrous matrices. Biomaterials. 2014 Feb;**35**(5):1496-1506. DOI: 10.1016/j.biomaterials.2013.11.013. Epub 2013 Nov 20

[6] Chan LS, Lapiere J, Chen M, Traczyk T, Mancini AJ, Paller AS, Woodley DT, Marinkovich MP. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Archives of Dermatology. 1999;**135**:569-573. DOI: 10.1001/archderm.135.5.569

[7] Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. Clinics in Dermatology. 2014;**32**:364-375. DOI: 10.1016/j.clindermatol.2013.11.003

[8] Vassileva S. Bullous systemic lupus erythematosus. Clinics in Dermatology. 2004;**22**:129-138. Review. DOI: 10.1016/j.clindermatol.2003.12.020

[9] Oke V, Wahren-Herlenius M. Cutaneous lupus erythematosus: Clinical aspects and molecular pathogenesis. Journal of Internal Medicine. 2013;**273**:544-554. DOI: 10.1111/joim.12057

[10] Boddu P, Nadiri M, Malik O. Diffuse bullous eruptions in an elderly woman: Late-onset bullous systemic lupus erythematosus. Case Reports in Dermatology. 2016;**8**:278-282. DOI: 10.1159/000448392

[11] Lourenço DM, Gomes RC, Aikawa NE, Campos LM, Romiti R, Silva CA. Childhood-onset bullous systemic lupus erythematosus. Lupus. 2014 Nov;**23**:1422-1425. DOI: 10.1177/0961203314544187

[12] Momen T, Madihi Y. Bullous systemic lupus erythematosus and lupus nephritis in a young girl. Oman Medical Journal. 2016;**31**:453-455. DOI: 10.5001/omj.2016.91

[13] Rassbach C, Shah N, Davis A. A 6-year-old girl with extensive bullous skin lesions. Pediatric Annals. 2012 Jun;**41**:229-231. DOI: 10.3928/00904481-20120525-05

[14] Tebbe B. Clinical course and prognosis of cutaneous lupus erythematosus. Clinics in Dermatology. 2004 Mar-Apr;**22**:121-124. Review. DOI: 10.1016/j.clindermatol.2003.12.018

[15] Contestable JJ, Edhegard KD, Meyerle JH. Bullous systemic lupus erythematosus: A review and update to diagnosis and treatment. American Journal of Clinical Dermatology. 2014 Dec;**15**:517-524. Review. DOI: 10.1007/s40257-014-0098-0

[16] Uva L, Miguel D, Pinheiro C, Freitas JP, Marques Gomes M, Filipe P. Cutaneous manifestations of systemic lupus erythematosus. Autoimmune Diseases. 2012;**2012**:834291. DOI: 10.1155/2012/834291

[17] Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus. 2010;**19**:1050-1070. DOI: 10.1177/0961203310370048

[18] Yogarajah M, Sivasambu B, Jaffe EA. Bullous systemic lupus erythematosus associated with esophagitis dissecans superficialis. Case Reports in Rheumatology. 2015;**2015**:930683. DOI: 10.1155/2015/930683

[19] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheumatism. 1997;**40**:1725. DOI: 10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y

[20] Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis and Rheumatism. 2012;**64**:2677-2686. DOI: 10.1002/art.34473

[21] Fujimoto W, Hamada T, Yamada J, Matsuura H, Iwatsuki K. Bullous systemic lupus erythematosus as an initial manifestation of SLE. The Journal of Dermatology. 2005 Dec;**32**:1021-1027. DOI: 10.1111/j.1346-8138.2005.tb00894.x

[22] Gual A, Guilabert A, Iranzo P, Flores G, Diaz LA, Mascaro JM Jr. IgG autoantibody subclass analysis as a tool to differentiate epidermolysis bullosa acquisita with overlapping

features of bullous systemic lupus erythematosus. Journal of the American Academy of Dermatology. 2013;**69**:34-36. DOI: 10.1016/j.jaad.2013.01.025

[23] Bernard P, Prost C, Aucouturier P, Durepaire N, Denis F, Bonnetblanc JM. The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. Journal of Investigative Dermatology. 1991;**97**:259-263. DOI: 10.1111/1523-1747.ep12480369

[24] Ranario JS, Smith JL. Bullous lesions in a patient with systemic lupus erythematosus. Journal of Clinical and Aesthetic Dermatology. 2014 Sep;**7**:44-49. PMCID: PMC4174920

[25] Sáez-de-Ocariz M, Espinosa-Rosales F, López-Corella E, de León-Bojorge B, Sáez-de-Ocariz M. Bullous lesions as a manifestation of systemic lupus erythematosus in two Mexican teenagers. Pediatric Rheumatology Online Journal. 2010;**8**:19. DOI: 10.1186/1546-0096-8-19

[26] Tromovitch TA, Hyman AB. Systemic lupus erythematosus with hemorrhagic bullae. Archives of Dermatology. 1961;**83**:64-68

[27] Hall RP, Lawley TJ, Smith HR, Bullous KSI. Eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. Annals of Internal Medicine. 1982;**97**:165-170. DOI: 10.7326/0003-4819-97-2-165

[28] Shirahama S, Furukawa F, Yagi H, Tanaka T, Hashimoto T, Takigawa M. Bullous systemic lupus erythematosus: Detection of antibodies against noncollagenous domain of type VII collagen. Journal of the American Academy of Dermatology. 1998;**38**:844-848. DOI: 10.1016/S0190-9622(98)70472-4

[29] Chen M, Doostan A, Bandyopadhyay P, Remington J, Wang X, Hou Y, et al. The cartilage matrix protein subdomain of type VII collagen is pathogenic for epidermolysis bullosa acquisita. The American Journal of Pathology. 2007;**170**:2009e18. DOI: 10.2353/ajpath.2007.061212

[30] Gammon WR, Briggaman RA, Bullous SLE. A phenotypically distinctive but immunologically heterogeneous bullous disorder. Journal of Investigative Dermatology. 1993;**100**:28-34. DOI: 10.1038/jid.1993.20

[31] Recke A, Sitaru C, Vidarsson G, Evensen M, Chiriac MT, Ludwig RJ, Zillikens D. Pathogenicity of IgG subclass autoantibodies to type VII collagen: Induction of dermal-epidermal separation. Journal of Autoimmunity. 2010;**34**:435-444. DOI: 10.1016/j.jaut.2009.11.003

[32] Shimanovich I, Mihai S, Oostingh GJ, Ilenchuk TT, Bröcker EB, Opdenakker G, Zillikens D, Sitaru C. Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquisita and bullous pemphigoid. The Journal of Pathology. 2004 Dec;**204**:519-527. DOI: 10.1002/path.1674

[33] Sitaru C, Mihai S, Otto C, Chiriac MT, Hausser I, Dotterweich B, Saito H, Rose C, Ishiko A, Zillikens D. Induction of dermal-epidermal separation in mice by passive transfer of

antibodies specific to type VII collagen. The Journal of Clinical Investigation. 2005 Apr;**115**:870-878. DOI: 10.1172/JCI200521386

[34] Chiriac MT, Roesler J, Sindrilaru A, Scharffetter-Kochanek K, Zillikens D, Sitaru C. NADPH oxidase is required for neutrophil-dependent autoantibody induced tissue damage. The Journal of Pathology. 2007;**212**:56-65. DOI: 10.1002/path.2157

[35] Aoki V, Sousa JX Jr, Fukumori LM, Perigo AM, Freitas EL, Oliveira ZN. Direct and indirect immunofluorescence. Anais Brasileiros de Dermatologia. 2010;**85**:490-500. DOI: 10.1590/S0365-05962010000400010

[36] Tatnall FM, Whitehead PC, Black MM, Wojnarowska F, Leigh IM. Identification of the epidermolysis bullosa acquisita antigen by LH7.2 monoclonal antibody: Use in diagnosis. The British Journal of Dermatology. 1989;**120**:533-539. DOI: 10.1111/j.1365-2133.1989.tb01327.x

[37] Komorowski L, Muller R, Vorobyev A, Probst C, Recke A, Jonkman MF, Hashimoto T, Kim SC, Groves R, Ludwig RJ, Zillikens D, Stöcker W, Schmidt E. Sensitive and specific assays for routine serological diagnosis of epidermolysis bullosa acquisita. Journal of the American Academy of Dermatology. 2013;**68**:89-95. DOI: 10.1016/j.jaad.2011.12.032

[38] Dotson AD, Raimer SS, Pursley TV, Tschen J. Systemic lupus erythematosus occurring in a patient with epidermolysis bullosa acquisita. Archives of Dermatology. 1981;**117**:422-426. DOI: 10.1001/archderm.1981.01650070050025

[39] McHenry PM, Dagg JH, Tidman MJ, Lever RS. Epidermolysis bullosa acquisita occurring in association with systemic lupus erythematosus. Clinical and Experimental Dermatology. 1993 Jul;**18**:378-380. DOI: 10.1111/j.1365-2230.1993.tb02224.x

[40] Oostingh GJ, Sitaru C, Zillikens D, Kromminga A, Luhrs H. Subclass distribution of type VII collagen-specific autoantibodies in patients with inflammatory bowel disease. Journal of Dermatological Science. 2005;**37**:182-184. DOI: 10.1016/j.jdermsci.2004.11.010

[41] Herrero-Gonzalez JE, Mascaro JM Jr, Herrero C, Dilling A, Zillikens D, Sitaru C. Autoantibodies from patients with BSLE inducing recruitment of leukocytes to the dermoepidermal junction and subepidermal splits in cryosections of human skin. Archives of Dermatology. 2006;**142**:1513-1516. DOI: 10.1001/archderm.142.11.1513

[42] Sitaru C, Kromminga A, Hashimoto T, Brocker EB, Zillikens D. Autoantibodies to type VII collagen mediate Fcgamma-dependent neutrophil activation and induce dermal-epidermal separation in cryosections of human skin. The American Journal of Pathology. 2002;**161**:301-311. DOI: 10.1016/S0002-9440(10)64182-X

[43] Malcangi G, Brandozzi G, Giangiacomi M, Zampetti M, Danieli MG. Bullous SLE: Response to methotrexate and relationship with disease activity. Lupus. 2003;**12**:63-66. DOI: 10.1191/0961203303lu241cr

[44] Miyagawa S, Shiomi Y, Fukumoto T, Nishikawa K, Ako H, Hashimoto T, Shirai T. Bullous eruption of systemic lupus erythematosus. The Journal of Dermatology. 1994 Jun;**21**:421-425. DOI: 10.1111/j.1346-8138.1994.tb01766.x

[45] Camisa C, Sharma HM. Vesiculobullous systemic lupus erythematosus. Report of two cases and a review of the literature. Journal of the American Academy of Dermatology. 1983;**9**:924-933. DOI: 10.1016/S0190-9622(83)70210-0

[46] Mekouar F, Hammi S, Elomri N, Ghafir D. Bullous systemic lupus erythematosus. Internal Medicine. 2011;**50**:1445. DOI: 10.2169/internalmedicine.50.4887

[47] Hamminga EA, Vermeer MH. Bullous systemic lupus erythematosus responding to mycophenolate mofetil. European Journal of Dermatology. 2010;**20**:844-845. DOI: 10.1684/ejd.2010.1081

[48] Barbosa WS, Rodarte CM, Guerra JG, Maciel VG, Fleury Junior LF, Bullous CMB. Systemic lupus erythematosus: Differential diagnosis with dermatitis herpetiformis. Anais Brasileiros de Dermatologia. 2011;**86**:92-95. DOI: 10.1590/S0365-05962011000700024

[49] Burke KR, Green BP, Meyerle J. Bullous lupus in an 18-year-old. Pediatric Dermatology. 2011;**28**:483. DOI: 10.1111/j.1525-1470.2011.01502.x

[50] Tincopa M, Puttgen KB, Sule S, Cohen BA, Gerstenblith MR. Bullous lupus: An unusual initial presentation of systemic lupus erythematosus in an adolescent girl. Pediatric Dermatology. 2010;**27**:373-376. DOI: 10.1111/j.1525-1470.2010.01179.x

[51] Pedro SD, Dahl MV. Direct immunofluorescence of bullous systemic lupus erythematosus. Archives of Dermatology. 1973 Jan;**107**:118-120. DOI: 10.1001/archderm.1973.01620160086028

[52] Onetti Muda A, Ruzzi L, Bernardini S, Teti A, Faraggiana T. Collagen VII expression in glomerular sclerosis. The Journal of Pathology. 2001 Oct;**195**:383-390. DOI: 10.1002/path.962

[53] Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: Revised criteria for diagnosis. The British Journal of Dermatology. 1995;**132**:921-928. DOI: 10.1111/j.1365-2133.1995.tb16950.x

[54] Camisa C. Vesiculobullous systemic lupus erythematosus. A report of four cases. Journal of the American Academy of Dermatology. 1988;**18**:93-100. DOI: 10.1016/S0190-9622(88)70014-6

[55] Bain EE, Grover RK, Plunkett RW, Beutner EH. Detection of collagen VII autoantibodies to NC1 and NC2 domains of collagen VII by ELISA in suspected epidermolysis bullosa acquisita and bullous lupus erythematosus patients. Journal of Dermatological Science. 2012;**65**:155-156. DOI: 10.1016/j.jdermsci.2011.12.004

[56] Gupta R, Woodley DT, Chen M. Epidermolysis bullosa acquisita. Clinics in Dermatology. 2012 Jan-Feb;**30**:60-69. DOI: 10.1016/j.clindermatol.2011.03.011

[57] Ludwig RJ. Clinical presentation, pathogenesis, diagnosis, and treatment of epidermolysis bullosa acquisita. ISRN Dermatology. 2013 Jul 15;**2013**:812029. DOI: 10.1155/2013/812029

[58] Ljubojevic S, Lipozenčić J. Autoimmune bullous diseases associations. Clinics in Dermatology. 2012;**30**:17-33. DOI: 10.1016/j.clindermatol.2011.03.006

[59] Barton DD, Fine JD, Gammon WR, Sams WM Jr. Bullous systemic lupus erythematosus: An unusual clinical course and detectable circulating autoantibodies to the epidermolysis bullosa acqusita antigen. Journal of the American Academy of Dermatology. 1986;**15**:369-373. DOI: 10.1016/S0190-9622(86)70181-3

[60] Hammers CM, Stanley JR. Mechanisms of disease: Pemphigus and bullous pemphigoid. Annual Review of Pathology. 2016;**11**:175-197. DOI: 10.1146/annurev-pathol-012615-044313

[61] Zhao CY, Murrell DF. Advances in understanding and managing bullous pemphigoid. F1000 Research. 2015;**4**:F1000 Faculty Rev-1313. DOI: 10.12688/f1000research.6896.1

[62] Ziemer M, Kardaun SH, Liss Y, Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: A descriptive study of 17 cases from a national registry and review of the literature. The British Journal of Dermatology. 2012 Mar;**166**:575-600. DOI: 10.1111/j.1365-2133.2011.10705.x

[63] Torchia D, Romanelli P, Kerdel FA. Erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis associated with lupus erythematosus. Journal of the American Academy of Dermatology. 2012 Sep;**67**:417-421. DOI: 10.1016/j.jaad.2011.10.012

[64] Patrício P, Ferreira C, Gomes MM, Filipe P. Autoimmune bullous dermatoses: A review. Annals of the New York Academy of Sciences. 2009 Sep;**1173**:203-210. DOI: 10.1111/j.1749-6632.2009.04737.x

[65] Daulatabadkar B, Pande S, Borkar M. Generalized bullous fixed drug reaction: A close similarity to Stevens-Johnson syndrome. Indian Journal of Drugs in Dermatology. 2017; **3**:28-31. DOI: 10.4103/ijdd.ijdd_11_17

[66] Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. Mayo Clinic Proceedings. 2010;**85**:131-138. DOI: 10.4065/mcp.2009.0379

[67] Horne NS, Narayan AR, Young RM, Frieri M. Toxic epidermal necrolysis in systemic lupus erythematosus. Autoimmunity Reviews. 2006;**5**:160-164. DOI: 10.1016/j.autrev.2005.10.003

[68] Ting W, Stone MS, Racila D, et al. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic pan-epidermolysis (ASAP): A case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. Lupus. 2004;**13**(12):941-950. DOI: 10.1191/0961203304lu2037sa

[69] Korponay-Szabó IR, Halttunen T, Szalai Z, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut. 2004;**53**:641-648. DOI: 10.1136/gut.2003.024836

[70] Kárpáti S. Dermatitis herpetiformis. Clinics in Dermatology. 2012 Jan-Feb;**30**:56-59. Review. DOI: 10.1016/j.clindermatol.2011.03.010

[71] Mendes FB, Hissa-Elian A, Abreu MA, Gonçalves VS. Review: Dermatitis herpetiformis. Anais Brasileiros de Dermatologia. 2013 Jul-Aug;**88**:594-599. DOI: 10.1590/abd1806-4841.20131775

[72] Grainge MJ, West J, Solaymani-Dodaran M, Card TR, Logan RF. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: A cohort study. Alimentary Pharmacology & Therapeutics. 2012 Mar;**35**:730-739. DOI: 10.1111/j.1365-2036.2012.04998.x

[73] Allen J, Wojnarowska F. Linear IgA disease: The IgA and IgG response to dermal antigens demonstrates a chiefly IgA response to LAD285 and a dermal 180-kDa protein. The British Journal of Dermatology. 2003;**149**:1055-1058. DOI: 10.1111/j.1365-2133.2003.05648.x

[74] Lee SYR, Leung CY, Leung CW, Chow CB, Leung KM, Lee QU. Linear IgA bullous dermatosis in a neonate. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2004;**89**:F280. DOI: 10.1136/adc.2003.037911

[75] Tobon GJ, Toro CE, Bravo JC, Canas CA. Linear IgA bullous dermatosis associated with systemic lupus erythematosus: A case report. Clinical Rheumatology. 2008;**27**:391-393. DOI: 10.1007/s10067-007-0752-5

[76] Shipman AR, Reddy H, Wojnarowska F. Association between the subepidermal autoimmune blistering diseases linear IgA disease and the pemphigoid group and inflammatory bowel disease: Two case reportsand literature review. Clinical and Experimental Dermatology. 2012;**37**:461-468. DOI: 10.1111/j.1365-2230.2012.04383.x

[77] Thune P, Eeg-Larsen T, Nilsen R. Acute linear IgA dermatosis in a child following varicella. Archives of Dermatology. 1984;**120**:1237-1238. DOI: 10.1001/archderm.1984.01650450119034

[78] Hollo P, Preisz K, Nemes L, Biro J, Karpati S, Horvath A. Linear IgA dermatosis associated with chronic clonal myeloproliferative disease. International Journal of Dermatology. 2003;**42**:143-146. DOI: 10.1046/j.1365-4362.2003.01438_2.x

[79] Collier PM, Wojnarowska F. Drug-inducer linear immunoglobulin A disease. Clinics in Dermatology. 1993;**11**:529-533. DOI: 10.1016/0738-081X(93)90161-5

[80] Girao L, Fiadeiro T, Rodrigues JC. Burn-induced linear IgA dermatosis. Journal of the European Academy of Dermatology and Venereology. 2000;**14**:507-510. DOI: 10.1046/j.1468-3083.2000.00158.x

[81] Egan CA, Zone JJ. Linear IgA bullous dermatosis. International Journal of Dermatology. 1999;**38**:818-827. DOI: 10.1046/j.1365-4362.1999.00813.x

[82] Pastuszczak M, Lipko-Godlewska S, Jaworek AK, Wojas-Pelc A. Drug-induced linear IgA bullous dermatosis after discontinuation of cefuroxime axetil treatment. Journal of Dermatological Case Reports. 2012;**6**:117-119. DOI: 10.3315/jdcr.2012.1119

[83] Fortuna G, Marinkovich MP. Linear immunoglobulin A bullous dermatosis. Clinics in Dermatology. 2012 Jan-Feb;**30**:38-50. DOI: 10.1016/j.clindermatol.2011.03.008

[84] Kettler AH, Bean SF, Duffy JO, Gammon WR. Systemic lupus erythematosus presenting as a bullous eruption in a child. Archives of Dermatology. 1988;**124**:1083-1087. DOI: 10.1001/archderm.1988.01670070071023

[85] Alarcón GS, Sams WM Jr, Barton DD, Reveille J. Bullous lupus erythematosus rash worsened by Dapsone. Arthritis and Rheumatism. 1984 Sep;**27**:1071-1072. DOI: 10.1002/art.1780270922

[86] Pilcher MF, Metzinger AR, Davis LS. Generalized bullous eruption in a teenager. Pediatric Dermatology. 2010;**27**:197-198. DOI: 10.1111/j.1525-1470.2010.01117.x

[87] Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: Overview and update. Journal of the American Academy of Dermatology. 2001;**45**:420-434. DOI: 10.1067/mjd.2001.114733

[88] Alahlafi AM, Wordsworth P, Wojnarowska F. The lupus band: Do the autoantibodies target collagen VII? The British Journal of Dermatology. 2004;**150**:504-510. DOI: 10.1046/j.1365-2133.2003.05738.x

[89] Alsanafi S, Kovarik C, Mermelstein A, Werth VP. Rituximab in the treatment of bullous systemic lupus erythematosus. Journal of Clinical Rheumatology. 2011;**17**:142-144. DOI: 10.1097/RHU.0b013e318214f30c

[90] Anyanwu CO, Ang CC, Werth VP. Oral mucosal involvement in bullous lupus. Arthritis and Rheumatism. 2013;**65**:2622. DOI: 10.1002/art.38051

[91] Pehr K. Mycophenolate mofetil and erythromycin for bullous lupus erythematosus of childhood. Journal of Cutaneous Medicine and Surgery. 2012;**16**:50-53. DOI: 10.1177/120347541201600110

[92] Farley-Li J, Mancini AJ. Treatment of linear IgA bullous dermatosis of childhood with mycophenolate mofetil. Archives of Dermatology. 2003;**139**:1121-1124. DOI: 10.1001/archderm.139.9.1121

[93] Tran MM, Anhalt GJ, Barrett T, Cohen BA. Childhood IgA mediated epidermolysis bullosa acquisita responding to mycophenolate mofetil as a corticosteroid-sparing agent. Journal of the American Academy of Dermatology. 2006;**54**:734. DOI: 10.1016/j.jaad.2005.07.009

[94] Fujinaga S, Ohtomo Y, Hara S, et al. Maintenance therapy with mycophenolate mofetil for children with severe lupus nephritis after low-dose intravenous cyclophosphamide regimen. Pediatric Nephrology. 2008;**23**:1877-1882. DOI: 10.1007/s00467-008-0800-7

[95] Samad AS, Lindsley CB. Treatment of pulmonary hemorrhage in childhood systemic lupus erythematosus with mycophenolate mofetil. Southern Medical Journal. 2003;**96**:705-707. DOI: 10.1097/01.SMJ.0000054424.20202.7D

[96] Kumar S, Agarwal I. Unusual presentation of childhood systemic lupus erythematosus. Pediatric Rheumatology Online Journal. 2007;**5**:20. DOI: 10.1186/1546-0096-5-20

[97] Juhász M, Rogge M, Chen M, Czernik A, Jung Kim S, Geller L. Case of pediatric bullous systemic lupus erythematosus treated with intravenous immunoglobulin. Pediatric Dermatology. 2017 Jan;**34**:54-56. DOI: 10.1111/pde.13015

[98] Czernik A, Toosi S, Bystryn JC, Grando SA. Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: An update. Autoimmunity. 2012;**45**:111-118. DOI: 10.3109/08916934.2011.606452

[99] Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: Definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Archives of Dermatology. 2002;**138**:370-379. DOI: 10.1001/archderm.138.3.370

[100] Chan LS. Ocular and oral mucous membrane pemphigoid.(cicatricial pemphigoid). Clinics in Dermatology. 2012;**30**:34-37. DOI: 10.1016/j.clindermatol.2011.03.007

[101] Xu HH, Werth VP, Parisi E, et al. Mucous membrane pemphigoid. Dental Clinics of North America. 2013;**57**(4):611-630. DOI: 10.1016/j.cden.2013.07.003

[102] Jolliffe DS, Sim-Davis D. Cicatricial pemphigoid in a young girl: Report of a case. Clinical and Experimental Dermatology. 1977;**2**:281-284. DOI: 10.1111/j.1365-2230.1977.tb02570.x

[103] Rogers M, Painter D. Cicatricial pemphigoid in a four-year-old child: A case report. The Australasian Journal of Dermatology. 1981;**22**:21-23. DOI: 10.1111/j.1440-0960.1981.tb00773.x

[104] Kharfi M, Khaled A, Anane R, et al. Early onset childhood cicatricial pemphigoid: A case report and review of the literature. Pediatric Dermatology. 2010;**27**:119-124. DOI: 10.1111/j.1525-1470.2009.01079.x

[105] Chan LS, Hammerberg C, Cooper KD. Significantly increased occurrence of HLA-DQB1*0301 allele in patients with ocular cicatricial pemphigoid. The Journal of Investigative Dermatology. 1997;**108**:129-132. DOI: on22-202X/97

[106] Bertram F, Brocker EB, Zillikens D, et al. Prospective analysis of the incidence of autoimmune bullous disorders in lower Franconia, Germany. Journal der Deutschen Dermatologischen Gesellschaft. 2009;**7**:434-440. DOI: 10.1111/j.1610-0387.2008.06976.x

[107] Bernard P, Antonicelli F, Bedane C, et al. Prevalence and clinical significance of anti-laminin 332 autoantibodies detected by a novel enzyme linked immunosorbent assay in mucous membrane pemphigoid. JAMA Dermatology. 2013;**149**:533-540. DOI: 10.1001/jamadermatol.2013.1434

[108] Rauz S, Maddison PG, Dart JKG. Evaluation of mucous membrane pemphigoid with ocular involvement in young patients. Ophthalmology. 2005;**112**:1268-1274. DOI: 10.1016/j.ophtha.2005.01.039

[109] Hübner F, Recke A, Zillikens D, Linder R, Schmidt E. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. The Journal of Investigative Dermatology. 2016;**136**(12):2495-2498. DOI: 10.1016/j.jid.2016.07.013

[110] Singh AP, Chaitra TR, Ravishankar TL, Singh SP, Mohapatra AK. HIV patient with mucous membrane pemphigoid: A case report. Ethiopian Journal of Health Sciences. 2014;**24**(2):179-182. PMC4006214

[111] Sezin T, Egozi E, Hillou W, Avitan-Hersh E, Bergman R. Anti-laminin-332 mucous membrane pemphigoid developing after a diphtheria tetanus vaccination. JAMA Dermatology. 2013;**149**(7):858-862. DOI: 10.1001/jamadermatol.2013.741

[112] Hingorani M, Lightman S. Ocular cicatricial pemphigoid. Current Opinion in Allergy and Clinical Immunology. 2006;**6**(5):373-378. DOI: 10.1097/01.all.0000244799.33734.d4

[113] Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. Autoimmunity Reviews. 2014 Apr-May;**13**(4-5):482-489. DOI: 10.1016/j.autrev.2014.01.047

[114] Bruch-Gerharz D, Hertl M, Ruzicka T. Mucous membrane pemphigoid: Clinical aspects, immunopathological features and therapy. European Journal of Dermatology. 2007;**17**:191-200. DOI: 10.1684/ejd.2007.0148

[115] Carrozzo M, Dametto E, Fasano ME, et al. Interleukin-4RA gene polymorphism is associated with oral mucous membrane pemphigoid. Oral Diseases. 2014;**20**:275-280. DOI: 10.1111/odi.12106

[116] Borradori L, Koch PJ, Niessen CM, et al. The localization of bullous pemphigoid antigen 180 (BP180) in hemidesmosomes is mediated by its cytoplasmic domain and seems to be regulated by the b4 integrin subunit. The Journal of Cell Biology. 1997;**136**:1333-1347. PMID: 17478379

[117] Fontao L, Favre B, Riou S, et al. Interaction of the bullous pemphigoid antigen 1 (BP230) and desmoplakin with intermediate filaments is mediated by distinct sequences within their COOH terminus. Molecular Biology of the Cell. 2003;**14**:1978. DOI: 10.1091/mbc.E02-08-0548

[118] Lazarova Z, Hsu R, Yee C, Yancey KB. Antiepiligrin cicatricial pemphigoid represents an autoimmune response to subunits present in laminin 5 (alpha3beta3gamma2). The British Journal of Dermatology. 1998;**139**(5):791-797. DOI: 10.1046/j.1365-2133.1998.02502.x

[119] Bernauer W, Wright P, Dart JK, Leonard JN, Lightman S. The conjunctiva in acute and chronic mucous membrane pemphigoid. An immunohistochemical analysis. Ophthalmology. 1993;**100**:339-346. DOI: 10.1016/S0161-6420(93)31644-1

[120] Suelves AM, Zhao TZ, Siddique SS, Foster CS. Profile of local interleukin expression in a cohort of ocular cicatricial pemphigoid patients. Investigative Ophthalmology & Visual Science. 2012;**53**(13, 13):8112-8117. DOI: 10.1167/iovs.11-9322

[121] Kourosh AB, Yancey KB. Pathogenesis of mucous membrane pemphigoid. Dermatologic Clinics. 2011;**29**(3):479-484. DOI: 10.1016/j.det.2011.03.011

[122] Tauber J, Sainz de la Maza M, Foster CS. Systemic chemotherapy for ocular cicatricial pemphigoid. Cornea. 1991;**10**:185-195. DOI: 10.1097/00003226-199105000-00001

[123] Kourosh AS, Yancey KB. Therapeutic approaches to patients with mucous membrane pemphigoid. Dermatologic Clinics. 2011;**29**:637-641. DOI: 10.1016/j.det.2011.06.022

[124] Murrell DF, Marinovic B, Caux F, et al. Definitions and outcome measures for mucous membrane pemphigoid: Recommendations of an international panel of experts. Journal of the American Academy of Dermatology. 2015;**72**(1):168-174. DOI: 10.1016/j.jaad.2014.08.024

[125] Yancey KB. Cicatricial pemphigoid. In: Wolff K, Goldsmith LA, Katz SI, et al., editors. Dermatology in General Medicine. 8th ed. New York: McGraw-Hill Inc; 2012. pp. 617-623

[126] Fueston JC, Adams BB, Cicatricial MDF. Pemphigoid-induced phimosis. Journal of the American Academy of Dermatology. 2002;**46**:128-129. DOI: 10.1067/mjd.2002.107967

[127] Marren P, Walkden V, Mallon E, Wojnarowska F. Vulval cicatricial pemphigoid may mimic lichen sclerosus. The British Journal of Dermatology. 1996;**134**:522-524. DOI: 10.1046/j.1365-2133.1996.43766.x

[128] Alexandre M, Brette MD, Pascal F, Tsianakas P, Fraitag S, Doan S, et al. A prospective study of upper aerodigestive tract manifestations of mucous membrane pemphigoid. Medicine (Baltimore). 2006;**85**:239-252. DOI: 10.1097/01.md.0000231954.08350.52

[129] Zehou O, Raynaud JJ, Le Roux-Villet C, et al. Oesophageal involvement in 26 consecutive patients with mucous membrane pemphigoid. The British Journal of Dermatology. 2017;**177**:1074-1085. DOI: 10.1111/bjd.15592

[130] Chan LS, Majmudar AA, Tran HH, Meier F, et al. Laminin-6 and laminin-5 are recognized by autoantibodies in a subset of cicatricial pemphigoid. The Journal of Investigative Dermatology. 1997;**108**:848-853. DOI: 10.1111/1523-1747.ep12292578

[131] Egan CA, Lazarova Z, Darling TN, et al. Anti-epiligrin cicatricial pemphigoid: Clinical findings, immunopathogenesis, and significant associations. Medicine (Baltimore). 2003; **82**:177-186. DOI: 10.1097/01.md.0000076003.64510.00

[132] Foster CS. Cicatricial pemphigoid. Transactions of the American Ophthalmological Society. 1986;**84**:527-663. PMCID: PMC1298749

[133] Yasukochi A, Teye K, Ishii N, Hashimoto T. Clinical and immunological studies of 332 Japanese patients tentatively diagnosed as anti-BP180-type mucous membrane pemphigoid: A novel BP180 C-terminal domain enzyme-linked immunosorbent assay. Acta Dermato-Venereologica. 2016;**96**(6):762-767. DOI: 10.2340/00015555-2407

[134] Bhol KC, Goss L, Kumari S, Colon JE, Ahmed AR. Autoantibodies to human alpha6 integrin in patients with oral pemphigoid. Journal of Dental Research. 2001;**80**(8):1711-1715. DOI: 10.1177/00220345010800080601

[135] Mobini N, Nagarwalla N, Ahmed AR. Oral pemphigoid. Subset of cicatricial pemphigoid? Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 1998;**85**(1):37-43. DOI: 10.1016/S1079-2104(98)90395-X

[136] Wojnarowska F, Marsden RA, Bhogal B, Black MM. Chronic bullous disease of childhood, childhood cicatricial pemphigoid, and linear IgA disease of adults. Journal of the American Academy of Dermatology. 1988;**19**:792-805. DOI: 10.1016/S0190-9622(88)70236-4

[137] Gibson V, Tschen JA, Bean SF. Localized cicatricial pemphigoid (Brunsting-Perry syndrome). Cutis. 1986;**38**:252-253

[138] Daito J, Katoh N, Asai J, et al. Brunsting-Perry cicatricial pemphigoid associated with autoantibodies to the C-terminal domain of BP180. The British Journal of Dermatology. 2008;**159**(4):984-986. DOI: 10.1111/j.1365-2133.2008.08753.x

[139] Joly P, Ruto F, Thomine E, et al. Brunsting-Perry cicatricial bullous pemphigoid: A clinical variant of localized acquired epidermolysis bullosa? Journal of the American Academy of Dermatology. 1993;**28**:89-92. DOI: 10.1016/0190-9622(93)70016-M

[140] Fleming TE, Korman NJ. Cicatricial pemphigoid. Journal of the American Academy of Dermatology. 2000;**43**(4):571-591. DOI: 10.1067/mjd.2000.107248

[141] Thorne JE, Anhalt GJ, Jabs DA, et al. Role of electron microscopy in the diagnosis of ocular mucous membrane pemphigoid. Ophthalmology. 2006;**113**:1651-1656. DOI: 10.1016/j.ophtha.2006.03.048

[142] Shimanovich I, Nitz JM, Zillikens D. Multiple and repeated sampling increases the sensitivity of direct immunofluorescence testing for the diagnosis of mucous membrane pemphigoid. Journal of the American Academy of Dermatology. 2017:31734-31736. DOI: 10.1016/j.jaad.2017.05.016

[143] Power WJ, Neves RA, Rodriguez A, et al. Increasing the diagnostic yield of conjunctival biopsy in patients with suspected ocular cicatricial pemphigoid. Ophthalmology. 1995;**102**:1158-1163. DOI: 10.1016/S0161-6420(95)30896-2

[144] Ali S, Kelly C, Challacombe SJ, et al. Salivary IgA and IgG antibodies to bullous pemphigoid 180 noncollagenous domain 16a as diagnostic biomarkers in mucous membrane pemphigoid. The British Journal of Dermatology. 2016;**174**(5):1022-1029. DOI: 10.1111/bjd.14351

[145] Amber KT, Bloom R, Hertl M. A systematic review with pooled analysis of clinical presentation and immunodiagnostic testing in mucous membrane pemphigoid: Association of anti-laminin-332 IgG with oropharyngeal involvement and the usefulness of ELISA. Journal of the European Academy of Dermatology and Venereology. 2016;**30**(1):72-77. DOI: 10.1111/jdv.13397

[146] Bekou V, Thoma-Uszynski S, Wendler O, et al. Detection of laminin 5-specific autoantibodies in mucous membrane and bullous pemphigoid sera by ELISA. The Journal of Investigative Dermatology. 2005;**124**:732-740. DOI: 10.1111/j.0022-202X.2005.23646.x

[147] Setterfield J, Shirlaw PJ, Bhogal BS, et al. Cicatricial pemphigoid: Serial titres of circulating IgG and IgA antibasement membrane antibodies correlate with disease activity. The British Journal of Dermatology. 1999;**140**:645-650. DOI: 10.1046/j.1365-2133.1999.02763.x

[148] Van Beek N, Rentzsch K, Probst C, Komorowski L, Kasperkiewicz M, Fechner K, et al. Serological diagnosis of autoimmune bullous skin diseases: Prospective comparison of the BIOCHIP mosaic-based indirect immunofluorescence technique with the conventional multi-step single test strategy. Orphanet Journal of Rare Diseases. 2012;**7**:49. DOI: 10.1186/1750-1172-7-49

[149] Oyama N, Setterfield JF, Powell AM, et al. Bullous pemphigoid antigen II (BP180) and its soluble extracellular domains are major autoantigens in mucous membrane pemphigoid: The pathogenic relevance to HLA class II alleles and disease severity. The British Journal of Dermatology. 2006 Jan;**154**(1):90-98. DOI: 10.1111/j.1365-2133.2005.06998.x

[150] Fania L, Giannico MI, Fasciani R, et al. Ocular mucous membrane pemphigoid after Lyell syndrome: Occasional finding or predisposing event? Ophthalmology. 2012;**119**(4):688-693. DOI: 10.1016/j.ophtha.2011.09.038

[151] Taylor J, McMillan R, Shephard M, et al. World workshop on oral medicine VI: A systematic review of the treatment of mucous membrane pemphigoid. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology. 2015;**120**(2):161-171. DOI: 10.1016/j.oooo.2015.01.024

[152] Michel JL, Gain P. Topical tacrolimus treatment for ocular cicatricial pemphigoid. Annales de Dermatologie et de Vénéréologie. 2006;**133**:161-164. DOI: AD-02-2006-133-2-0151-9638-101019-200517473

[153] Donnenfeld ED, Perry HD, Wallerstein A, et al. Subconjunctival mitomycin C for the treatment of ocular cicatricial pemphigoid. Ophthalmology. 1999;**106**:72-78. DOI: 10.1016/S0161-6420(99)90022-2

[154] Moghadam-Kia S, Werth VP. Prevention and treatment of systemic glucocorticoid side effects. International Journal of Dermatology. 2010;**49**:239-248. DOI: 10.1111/j.1365-4632.2009.04322.x

[155] Ciarrocca KN, Greenberg MS. A retrospective study of the management of oral mucous membrane pemphigoid with dapsone. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 1999;**88**:159-163. DOI: 10.1016/S1079-2104(99)70110-1

[156] Heffernan MP, Bentley DD. Successful treatment of mucous membrane pemphigoid with infliximab. Archives of Dermatology. 2006;**142**:1268-1270. DOI: 10.1001/archderm.142.10.1268

[157] Schulz S, Deuster D, Schmidt E, et al. Therapeutic effect of etanercept in anti-laminin 5 (laminin 332) mucous membrane pemphigoid. International Journal of Dermatology. 2011;**50**(9):1129-1131. DOI: 10.1111/j.1365-4632.2010.04707.x

[158] Papaliodis GN, Chu D, Foster CS. Treatment of ocular inflammatory disorders with daclizumab. Ophthalmology. 2003;**110**:786-789. DOI: 10.1016/S0161-6420(02)01932-2

[159] Shetty S, Ahmed AR. Critical analysis of the use of rituximab in mucous membrane pemphigoid: A review of the literature. Journal of the American Academy of Dermatology. 2013;**68**:499-506. DOI: 10.1016/j.jaad.2012.10.018

[160] Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. Archives of Dermatology. 2011;**147**:843-849. DOI: 10.1001/archdermatol.2011.54

[161] Foster CS, Chang PY, Ahmed AR. Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid: A preliminary report. Ophthalmology. 2010;**117**:861-869. DOI: 10.1016/j.ophtha.2009.09.049

[162] Tavakolpour S. The role of intravenous immunoglobulin in treatment of mucous membrane pemphigoid: A review of literature. Journal of Research in Medical Sciences. 2016;**21**:37. DOI: 10.4103/1735-1995.183992

[163] Bohn J, Jonsson S, Holst R. Successful treatment of recalcitrant cicatricial pemphigoid with a combination of plasma exchange and cyclophosphamide. The British Journal of Dermatology. 1999;**141**:536-540. DOI: 10.1046/j.1365-2133.1999.03054.x

Chapter 7

Histomorphologic and Direct Immunofluorescence Findings of Autoimmune Bullous Disease

Deniz Ates

Additional information is available at the end of the chapter

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Abstract

Autoimmune bullous diseases mainly present with vesiculobullous reaction pattern. First algorithm to approach skin biopsy of autoimmune vesiculobullous disease should be localization of the anatomic level of the split, which could be either intraepidermal or subepidermal. Second, inflammatory cell component should be evaluated, which could vary due to age of the lesion. Third, presence or absence of acantholysis should be considered. Finally, pattern of positive immunofluorescence results or negativity helps to render definitive diagnosis. In this chapter, practical histopathology and direct immunofluorescence findings of autoimmune bullous disease are discussed and supported by illustrative microphotographs taken from cases within our institution.

Keywords: histology, histopathology, autoimmune bullous disease, immunofluorescence, autoimmune vesiculobullous disease

1. Introduction

Autoimmune bullous diseases can be debilitating or even fatal. Therefore, disease control is crucial, and this cannot be achieved without a definitive diagnosis. One of the most important diagnostic tools is light microscopic findings with the additional support of immunofluorescence results. Furthermore, vesiculobullous reaction patterns can be seen in various dermatologic conditions. Histopathological assessment with clinical correlation is also important in ruling out nonautoimmune blistering disease.

To render a definitive result, the histomorphologist follows an algorithm starting with the exclusion of nonautoimmune blistering diseases with morphological and clinical findings.

Second, the anatomic level of the split should be localized, which could be either intraepidermal or subepidermal. Third, the predominant inflammatory cell component should be determined, which can vary due to age of the lesion. Then, additional pathologic features, such as presence or absence of acantholysis, should be considered. The combination of all clinical and histomorphological data with results of immunofluorescence assays and salt split tests is crucial for diagnosing autoimmune vesiculobullous diseases.

In this chapter, practical histomorphological and direct immunofluorescence findings on autoimmune blistering skin diseases are explained using illustrative microscopic photographs.

Autoimmune bullous diseases are classified as follows:

1. Pemphigus group

- **a.** Pemphigus vulgaris
- **b.** Pemphigus vegetans
- **c.** Pemphigus foliaceus
- **d.** Pemphigus erythematosus
- **e.** Endemic pemphigus
- **f.** IgA pemphigus
- **g.** Pemphigus herpetiformis
- **h.** Paraneoplastic pemphigus
- **i.** Drug-induced pemphigus

2. Subepidermal autoimmune bullous disease

- **a.** Subepidermal blisters with eosinophils
  - **i.** Bullous pemphigoid
  - **ii.** Gestational pemphigoid
- **b.** Subepidermal autoimmune bullous diseases with neutrophils
  - **i.** Dermatitis herpetiformis
  - **ii.** Linear IgA bullous dermatitis
  - **iii.** Mucous membrane (cicatricial) pemphigoid
  - **iv.** Anti-p200 pemphigoid
  - **v.** Bullous lupus erythematosus
  - **vi.** Epidermolysis bullosa acquisita

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2. Pemphigus group

2.1. Pemphigus vulgaris

Pemphigus vulgaris is a suprabasilar acantholytic vesiculobullous disease. Extension of a cleft formation throughout the adnexal epithelium is its characteristic. Basal cells lose their intercellular connections but retain dermal attachments. Hence, they attain their classical "tombstone" appearance (**Figure 1**). Split space usually contains detached acantholytic cells. Occasionally, a few eosinophils and neutrophils accompany acantholytic cells in the bulla cavity.

The early stages of pemphigus vulgaris, epidermal edema and intercellular bridges are lost at the epidermis and adnexal epithelium. One should be alerted for follicular acantholysis because it could be a clue for early diagnosis for pemphigus vulgaris. Early lesion may show eosinophilic spongiosis.

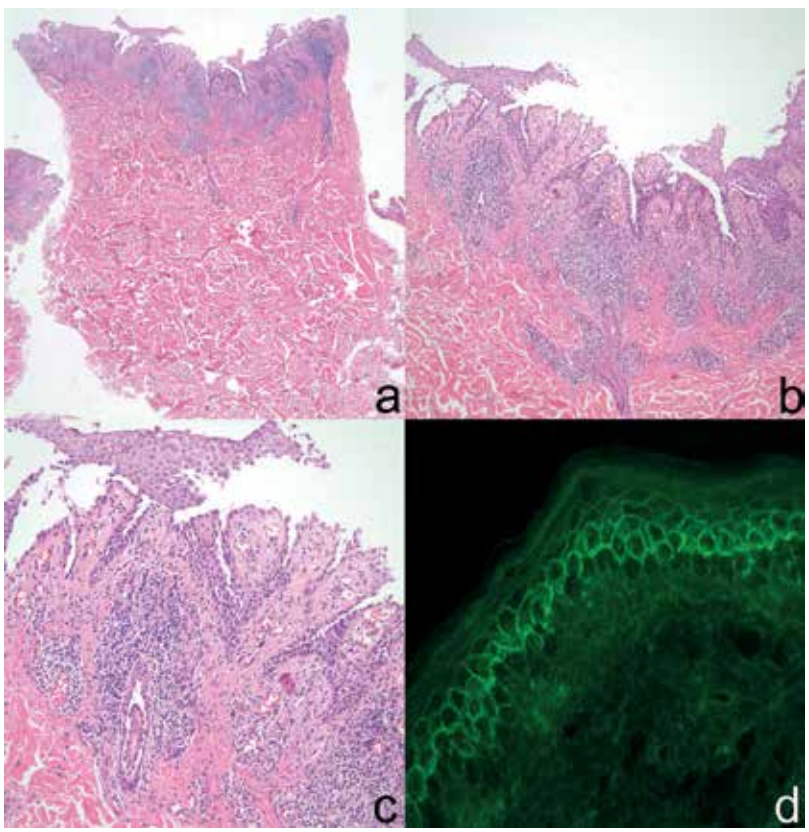

Figure 1. Pemphigus vulgaris. (a) Subrabasal split with few acantholytic cells (40×). (b) Classical "tombstone" appearance at the basal layer (100×). (c) Extention of subrabasal split throughout the adnexal epithelium (200×). (d) Intraepidermal IgG positivity mainly at the deep levels of the epidermis (400×).

The dermal level exhibits mild nonspecific changes such as mild perivascular dermatitis with mild mix inflammation usually containing eosinophils.

A biopsy should be taken from nonaffected perilesional area. Direct immunofluorescence shows intraepidermal intercellular IgG deposition predominantly in the lower portion (**Figure 1**). Less frequently, C3, IgM and IgA intercellular positivity is present. Outer root sheet of the anagen hair follicle may also be positive within intercellular area.

Application of C4d immunohistochemistry on routinely processed tissue sections could be a helpful tool for pemphigus vulgaris [1].

2.2. Pemphigus vegetans

Pemphigus vegetans is characterized by a vegetative histologic appearance caused by hyperkeratosis, acanthosis, papillomatosis and downward proliferation of rete ridges. On occasion, proliferation can be exuberant condition known as "pseudoepitheliomatous hyperplasia." Epidermal hyperplasia involves both the follicular epithelium and the epidermis. Characteristically, mild suprabasilar acantholysis and an intense collection of inflammatory infiltrate with neutrophils and eosinophils are present. The dermis contains a heavy infiltrate of lymphocytes, eosinophils and/or neutrophils.

Direct immunofluorescence findings are the same as those of pemphigus vulgaris, as both show intercellular deposition of IgG and/or C3.

2.3. Pemphigus foliaceus

Bullas of Pemphigus foliaceus are very fragile due to superficial splitting, thus, it is very difficult to obtain intact bulla. Biopsy taken from an established lesion reveals an upper granular or subcorneal split (**Figure 2**). In the bulla cavity, it is common to see acantholytic cells, fibrin and some neutrophils. Through careful examination, a pathologist can detect a focal acantholysis inside the follicular epithelium. When the bulla cavity contains neutrophils, other subcorneal blistering disorders (such as bullous impetigo, staphylococcal scaled skin syndrome, IgA pemphigus and subcorneal pustular dermatosis) will be in differential. Immunofluorescence will be helpful in making this distinction.

The superficial dermis could be edematous with a mixed inflammatory cell infiltrate.

There are some uncommon histologic features of pemphigus foliaceus, which are presented in **Table 1**.

Late lesions can show parakeratosis and acanthosis. Dyskeratotic cells resembling Darier's corps and rounds can accompany.

Direct immunofluorescence shows intercellular staining of IgG and C3 mostly at the higher levels of the epidermis.

Immunofluorescence is a helpful tool to differentiate other lichenoid-looking lesions in oral mucosa, and it is recommended to perform when a lichenoid lesion is detected [2].

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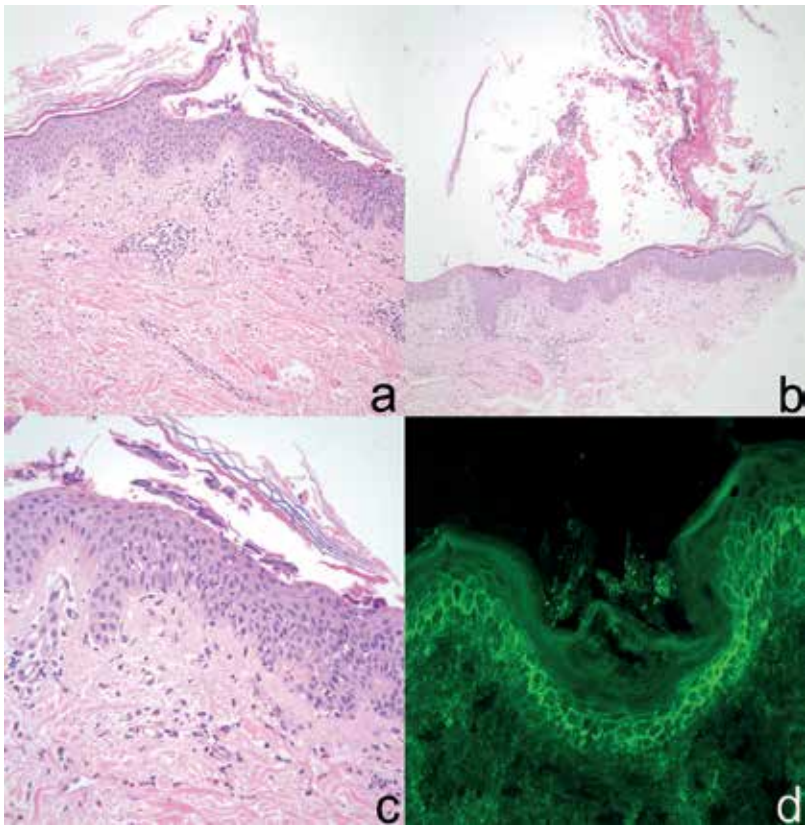

Figure 2. Pemphigus foliaceus. (a) Upper granular split (40×). (b) Fragile bulla is tearing off the upper epidermal layers (40×). (c) Acantholytic granular layer cells (200×). (d) Intraepidermal IgG positivity mainly at the superficial levels of the epidermis (200×).

Uncommon histological manifestation	More related disease
Neutrophilic spongiosis	IgA pemphigus
Neutfophilic pustules	IgA pemphigus
	Pustular psoriasis
	Bullous impetigo
	Subcorneal pustular dermatosis
Eosinophilic spongiosis	Endemic pemphigus

Table 1. Uncommon histologic features and more related disease of pemphigus foliaceus.

2.4. Pemphigus erythematosus

The H&E appearance of pemphigus erythematosus is almost the same as that of the pemphigus foliaceus (an upper granular or subcorneal split with acantholysis).

Direct immunofluorescence displays intercellular and dermoepidermal linear positivity of IgG and/or C3. The dermoepidermal positivity of IgG could be related to sun exposure [3].

2.5. Endemic pemphigus foliaceus (fogo selvagem)

Histological features are very similar to those of pemphigus foliaceus; a superficial split can be seen if non-bullous erosions are not biopsied. Early lesions typically show eosinophilic spongiosis. An established lesion can display inflammatory cells (mainly neutrophils) and a few acantholytic cells.

2.6. IgA pemphigus

Two major types are identified:

- Subcorneal pustular dermatosis (SPD) (IgA pemphigus foliaceus).
- Intraepidermal neutrophilic IgA dermatosis (IEN) (IgA pemphigus vulgaris).

In the SPD variant, vesicles are typically located at a subcorneal location. The bulla cavity is usually full of neutrophils (**Figure 3**). In the IEN, pustules can be found throughout all layers of the epidermis. Hair follicle involvement is also evident. Apart from the major two subtypes, patients with IgA pemphigus can show histomorphological features of *P. vulgaris*, *P. foliaceus* or pemphigus vegetans [4].

Direct immunofluorescence exhibits intraepidermal IgA positivity. SPD variant IgA deposition is at the superficial layers of epidermis, whereas in IEN variant fluorescence, it is seen throughout the epidermis.

2.7. Pemphigus herpetiformis

Inflammatory cell infiltrate (eosinophils, neutrophils or both) and acantholysis are usually prominent. Subcorneal or intraepidermal eosinophilic/spongiotic abscess formation is frequent. Pemphigus herpetiformis histomorphology usually presents as eosinophilic spongiosis.

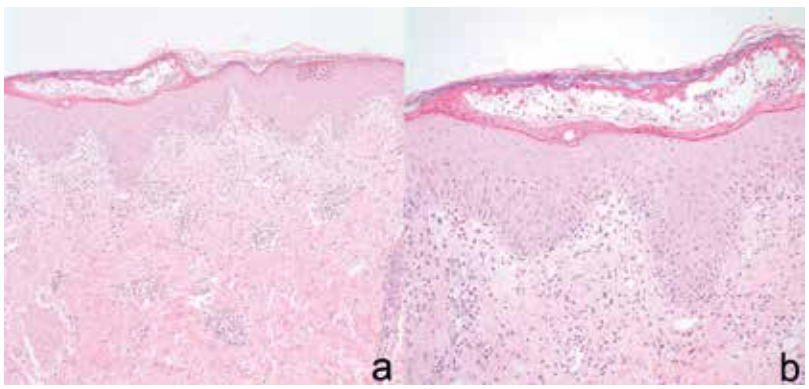

Figure 3. IgA pemphigus. (a) Intra/sub corneal vesicle (40×). (b) The bulla cavity is full of neutrophils (200×).

Direct immunofluorescence usually demonstrates IgG and/or C3 in the intercellular spaces [5].

2.8. Paraneoplastic pemphigus

The histomorphological findings of paraneoplastic pemphigus are highly variable.

Characteristically:

1. Suprabasal acantholysis with cleft of vesicle formation (resembles pemphigus foliaceus)
2. Interphase changes dense lymphohistiocytic infiltrate with basal degeneration and dyskeratotic cells
3. Spongiosis and lymphocyte exocytosis
4. Pigment incontinence is in evidence
5. Eosinophils are rare.

Some studies show that keratinocyte necrosis is associated with an adverse prognosis [3].

Direct immunofluorescence shows intercellular and linear basement membrane staining with C3 and IgG.

2.9. Drug-induced pemphigus

Subcorneal split, spongiosis with eosinophils, necrotic foci of keratinocytes, focal acantholysis are mentioned as histomorphologic findings of drug-induced pemphigus [6]. Unfortunately, drug-induced pemphigus is indistinguishable from idiopathic counterparts based on histomorphological and immunofluorescence findings [4].

Notably, vesiculobullous reaction patterns can be seen in many other dermatologic conditions. Histomorphologic evaluation should begin with exclusion of other diseases if possible and should consider other histologic features.

Nonautoimmune vesiculobullous diseases with subcorneal and intraepidermal split are given in **Table 2**.

Intracorneal and subcorneal blisters	İntraepidermal blisters	Suprabasilar blisters
Impetigo	Spongiotic blistering diseases	Hailey-Hailey
Staphlococcal "scalded skin" syndrome	Palmoplantar pustulosis	Darier's disease
Dermatophytosis	Erosive pustular dermatosis of the leg	Grover's disease
Subcorneal Pustular Dermatosis	Viral blistering Disease	Acantholytic solar keratosis
Infantile Acropustulosis	Friction Blister	
Erythema toxicum neonatorum		
Transient Neonatal Pustular Melanosis		
Acute Generalized Exanthematous Pustulosis		

Table 2. Non-autoimmune vesiculobullous diseases with subcorneal and intraepidermal split.

3. Subepidermal bullous disease

3.1. Subepidermal diseases with predominantly eosinophils

3.1.1. Bullous pemphigoid

A well-developed bullous pemphigoid blister is classically subepidermally located and is unilocular (**Figure 4**). Inflammatory cells are seen in the blister cavity, predominantly eosinophils. The dermal papillary outline is typically retained, and papillary dermal bulges are typically projected into the bulla cavity otherwise known as festooning. Bullous pemphigoid histological findings vary according to the duration of the lesion and the clinical appearance of the biopsy site.

If the biopsy is taken from apparently normal skin, a sparse dermal infiltrate is seen. However, when a biopsy is taken from a lesion with an erythematous base, a more prominent dermal infiltrate is seen sometimes accompanied by eosinophilic spongiosis. It is not unusual to see an eosinophilic flame in clinically erythematous-based lesions.

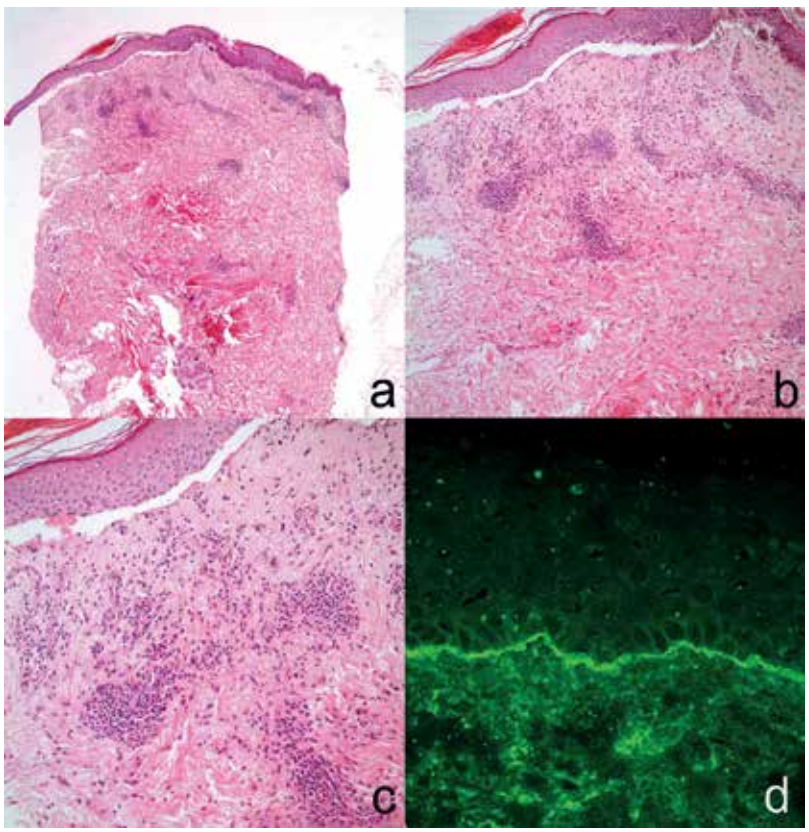

Figure 4. Bullous pemphigoid. (a) Unilocular subepidermal located split (40×). (b) Dermal papillary outline is typically retained (100×). (c) Predominantly eosinophilic dermal inflammatory infiltrate is seen (200×). (d) Homogenous linear positivity with IgG at the basal membrane zone.

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In lesions of several days duration, the blister may appear intraepidermal.

Prodromal lesions can show edema of the papillary dermis and a superficial perivascular dermatitis with eosinophils, neutrophils and lymphocytes is usually accompanied by an inflammatory component (**Figure 5**). An eosinophilic spongiosis pattern is also a well-known feature of early lesions of bullous pemphigoid. Occasionally, bullous pemphigoid lesions are accompanied by a predominance of neutrophils and aligned close to the basilar layer portion of the papillary dermis.

When direct immunofluorescence is applied to the biopsy from the perilesional area, it shows homogenous linear positivity with IgG and/or C3 at the basal membrane zone. Prodromal lesions may be positive with C3 only. IgA and IgM are positive in 20% of the cases [7].

Application of C4d immunohistochemistry on routinely processed tissue sections could be a helpful tool for bullous pemphigoid and confirms immunoreactant deposition [1, 8].

3.1.2. Gestational pemphigoid

A biopsy taken from an early lesion often shows the prominent dermal edema looking like a "teardrop." The edema consists of various inflammatory cells predominantly eosinophils. Tips of the dermal papilla consist of spongiosis and/or necrotic keratinocytes. The dermis underlying vesicle demonstrates a perivascular and interstitial inflammatory infiltrate mainly of eosinophils. Neutrophils, histiocytes and lymphocytes are the accompanying cell component. Neutrophils may also predominate.

Direct immunofluorescence will show C3 positivity, and 30–50% of cases show linear IgG positivity at the basal membrane zone [4].

Microscopic differential diagnosis in the early stages can include urticarial reactions and conditions associated with eosinophilic spongiosis. Without any clinical information, classical lesions are almost impossible to differentiate from bullous pemphigoid.

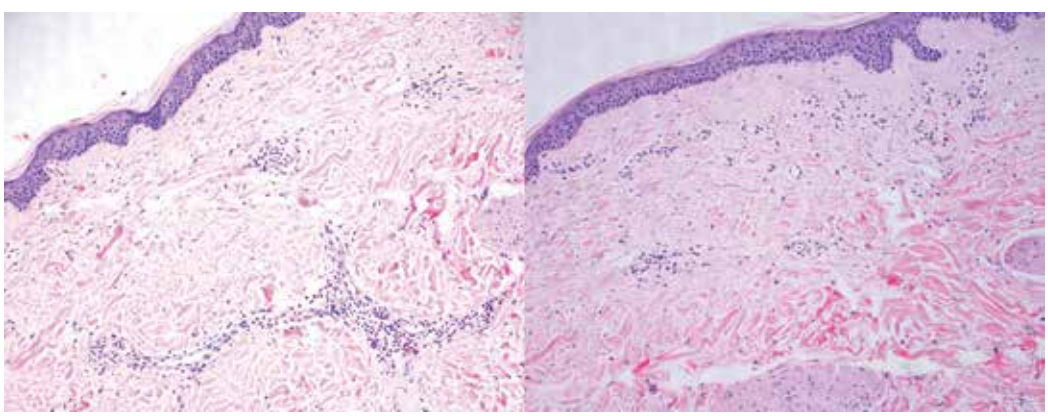

Figure 5. Urticarial phase of the bullous pemphigoid (100×). Edema of the papillary dermis and a superficial perivascular dermatitis with eosinophils.

3.2. Subepidermal diseases with predominantly neutrophils

3.2.1. Dermatitis herpetiformis (Duhring disease)

Biopsies taken from established bulla show subepidermal blisters with a dermal papillary neutrophilic microabscess, which is a hallmark histologic feature of dermatitis herpetiformis (**Figure 6**). Fibrin found at the tips of the dermal papilla forms a reticular network at the bulla cavity. When the duration of the lesion reaches to 38–48 h, neutrophilic consistency of bulla cavity decreases and eosinophils increase. The roof of the bulla cavity has usually smooth outline, contrast to the "festooning" pattern of the bullous pemphigoid.

At the dermis, mixed inflammatory cell infiltrate consists of abundant neutrophils. Leukocytoclasis and swelling of the endothelium are typical findings; however, vasculitis is not in evidence.

Elementary lesions of celiac disease in an intestinal mucosal biopsy occur due to an increase in intraepidermal lymphocytes and crypt hyperplasia and a decrease in villous height. These histological changes are reversed following a gluten-free diet.

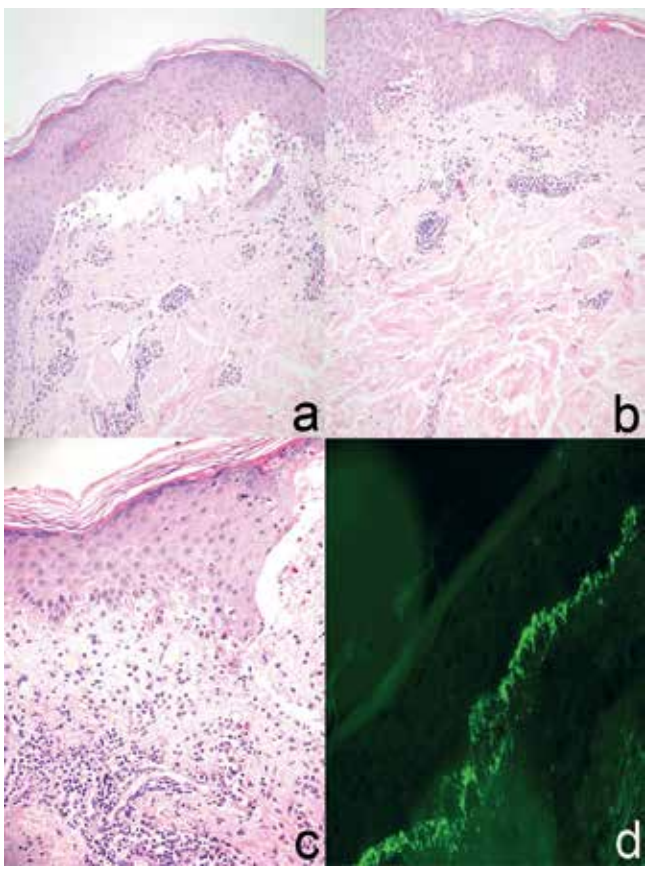

Figure 6. Dermatitis Herpetiformis. (a) Subepidermal split with reticular fibrin network (100×). (b) Dermal papillary microabcess (100×). (c) Eosinophilic consistency of the lesion (200×). (d) Granular IgA deposition in the dermal papillae (200×).

Direct skin immunofluorescence shows granular IgA deposition in the dermal papillae.

The histological differential diagnosis of dermatitis herpetiformis includes linear IgA disease, bullous pemphigoid and bullous lupus. Immunofluorescent studies are critical in making this distinction.

3.2.2. Linear IgA dermatosis

Linear IgA light microscopic features are subepidermal blisters with neutrophils; these frequently resemble dermatitis herpetiformis. The neutrophilic infiltrate is more localized to dermal papilla in dermatitis herpetiformis, whereas in linear IgA dermatosis neutrophils are more widespread. On occasion, eosinophils are also seen in the bulla cavity. The disease is rarely presented with eosinophilic spongiosis.

Direct immunofluorescence reveals homogenous linear IgA deposition along the basement membrane. In 80% of the cases, IgA is the only immunoreactant. IgG, IgM and C3 may also be present.

3.2.3. Mucous membrane pemphigoid

The mucous membrane pemphigoid consists of a varying number and consistency of inflammatory cells, depending on the age of the lesion. Lesions of less than 48 h duration, like dermatitis herpetiformis, present with dermal papillary microabscesses. As a lesion gets older, the neutrophil consistency of the infiltrate decreases and the eosinophil and latter lymphocyte content increases. Even in early lesions, if the biopsy corresponds to a previous bulla site, mucosal scar formation is in evidence.

The dermis contains perivascular lymphohistiocytic infiltrate accompanied by neutrophils, eosinophils and plasma cells. In late lesions, the superficial dermis shows scarring, with or without subepidermal split.

Direct immunofluorescence shows linear deposits of IgG and often C3 along the basement membrane. Positivity rate increases in buccal mucosa.

3.2.4. Anti p200 pemphigoid

It is a very rare subepidermal blistering disease. A study of 12 cases by Meijer JM et al. in 2014 found that subepidermal blistering is present in every case. An upper dermal infiltrate of eosinophils and neutrophils was seen in nearly all cases. Direct immunofluorescence results displayed IgG and C3 positivity in all cases [9].

3.2.5. Bullous lupus erythematosus

In bullous systemic lupus erythematosus, the findings are often identical to dermatitis herpetiformis. The blister cavity consists of fibrin and many neutrophils. Lymphocytes, histiocytes and eosinophils are occasionally seen. Nuclear dusts (leukocytoclastic debris) are evident in both bulla cavity and perivascular areas. Perivascular neutrophilic debris and the evidence of

vasculitis usually situated deeper than dermatitis herpetiformis. Vacuolar interphase change with dyskeratotic cells is occasional.

Classically, by using direct immunofluorescent test, the disease is characterized by the presence of IgG and C3 at the basement membrane. Pattern could be both linear and granular. Biopsy infrequently shows epidermal nuclear IgG staining, which is diagnostically very helpful staining. Concurrence of IgG, IgA and IgM positivity is not rare. Immunoreactants are also demonstrated at the vessel walls.

3.2.6. Epidermolysis bullosa acquisita

Classical pattern is a cell-free subepidermal blister. Disease can present with neutrophil (papillary microabscesses) or occasionally, eosinophil-rich infiltrate. Blister roof is usually intact, although some dermal fragments and fibrin may be displayed. PAS positivity is demonstrated at the bulla roof due to the basement membrane split.

Direct immunofluorescence shows linear deposition immunoglobulins particularly, IgG and C3 along the basement membrane.

Nonautoimmune vesiculobullous diseases with subepidermal split should always be in differential (**Table 3**).

Subepidermal blisters with little inflammation	**Subepidermal blisters with lymphocytes**	**Subepidermal blisters with eosinophils**	**Subepidermal blisters with neutrophils**
Porphyria cutanea tarda	Erythema multiforme	Arthropod bite	Bullous urticaria
Burns and cryotherapy	Paraneoplastic pemphigus	Drug reactions	Bullous acute vasculitis
Toxic epidermal necrolysis	Fixed drug eruption	Epidermolysis bullosa	Erysipelas
Suction blisters	Lichen sclerosus Et atrophicus		Sweet syndrome
Blisters overlying scars	Lichen planus pemphigoides		
Bullous solar elastosis	Polymorphic light eruption		
Bullous amyloidosis	Bullous lichen planus		
Bullous drug reaction	Bullous allergic contact dermatitis		

Table 3. Non-autoimmune vesiculobullous diseases with subepidermal split.

4. Salt split testing

This is a modified indirect immunofluorescence technique that aims to produce artificial split between lamina lucida and lamina densa of the basal membrane. The split roof is supposed to be covered by lamina lucida and the floor by lamina densa. Artificial splitting is obtained by

treating normal skin with a 10–15 ml 1 M NaCl solution for 48 h at 4°C. The direct technique then involves applying IgG to the tissue. Split testing with a saline application is commonly used in daily practice. Practical use of salt split test is summarized in **Table 4**.

Practical summary of histomorphology and immunofluorescent findings of autoimmune vesiculobullous diseases is given in **Table 5**.

Disease with supralamina densa split (roof labeling)	Disease with sublamina densa split (floor labeling)	Variable diseases
Bullous pemphigoid	Epidermolysis bullosa acquisita	Linear IgA
Pemphigoid gestationis	Bullous systemic lupus erythematosus	Mucosal pemphigoid (mostly supralamina densa-roof)

Table 4. Practical use of salt split technique in autoimmune vesiculobullous diseases.

Autoimmune disease	Target antigen	Anatomic localization and pattern of immunofluorescence	Anatomic localization of split	Staining of salt split test
Pemphigus vulgaris	Desmoglein-3	IgG and/or C3. İntraepidermal – predominantly basal	Suprabasal	N/A
Bullous pemphigoid	BPAg1, BPAg2	IgG and/or C3. Subepidermal- linear	Subepidermal	Roof
Dermatitis herpetiformis	Tissue transglutaminase	Granular IgA at the dermoepidermal junction	Subepidermal	N/A
Linear IgA bullous dermatitis	LABD97, LAD-1, LAD285	Linear IgA at the dermoepidermal junction	Subepidermal	Roof or floor or both
Bullous lupus erythematosus	Type VII collagen	Linear IgG, C3	Subepidermal	Floor
EBA	Type VII collagen	Linear IgG, C3	Subepidermal	Floor

Table 5. Summary of histomorphology and direct Immunofluorescent findings of autoimmune vesiculobullous diseases.

5. Indirect immunofluorescence

General rules for direct immunofluorescence testing are also valid for indirect immunofluorescence technique. A punch or excisional biopsy from perilesional skin or mucous membrane should be send to laboratory without fixative within a plastic tube or in isotonic NaCl solution. If the biopsy is planning to be sent elsewhere, biopsy can be placed in a Michel's solution [10]. This solution is also a well-established medium for polymerase chain reaction analysis [11]. Laboratory method is complicated than the direct method, so it is not preferred in daily routine practice. First, the patient serum should be prepared for testing. The blood sample is

needed to be centrifuged to separate the serum. A total of 4–6 micron thick slides are prepared from the biopsy, then, treated with prepared serum for 30 min. In case of titer requirement, doubling dilution is performed. Slides are washed, and then, the standardized fluorescein-labeled antibody binds to the serum antibody. It is examined under florescent microscope.

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References

[1] Villani AP, Chouvet B, Kanitakis J. Application of C4d immunohistochemistry on routinely processed tissue sections for the diagnosis of autoimmune bullous Dermatoses. The American Journal of Dermatopathology. 2016;**38**(3):186-188

[2] Yamanaka Y, Yamashita M, Innocentini LMA, Macedo LD, Chahud F, Ribeiro-Silva A, Roselino AM, Rocha MJA, Motta AC. Direct immunofluorescence as a helpful tool for the differential diagnosis of oral lichen Planus and oral Lichenoid lesions. The American Journal of Dermatopathology. 2017

[3] Oktarina DA, Poot AM, Kramer D, Diercks GF, Jonkman MF, Pas HH. The IgG "lupus-band" deposition pattern of pemphigus erythematosus: Association with the desmoglein 1 ectodomain as revealed by 3 cases. Archives of Dermatology. 2012;**148**(10):1173-1178

[4] Calonje E, Brenn T, Lazar A, McKee PH. McKee's Pathology of the Skin: With Clinical Correlations. 4th ed. Edinburgh: Elsevier/Saunders; 2011

[5] Leger S, Picard D, Ingen-Housz-Oro S, Arnault JP, Aubin F, Carsuzaa F, Chaumentin G, Chevrant-Breton J, Chosidow O, Crickx B, et al. Prognostic factors of paraneoplastic pemphigus. Archives of Dermatology. 2012;**148**(10):1165-1172

[6] Landau M, Brenner S. Histopathologic findings in drug-induced pemphigus. The American Journal of Dermatopathology. 1997;**19**(4):411-414

[7] Peters MS, Rogers RS. Clinical correlations of linear IgA deposition at the cutaneous basement membrane zone. Journal of the American Academy of Dermatology. 1989;**20** (5 Pt 1):761-770

[8] Chandler W, Zone J, Florell S. C4d immunohistochemical stain is a sensitive method to confirm immunoreactant deposition in formalin-fixed paraffin-embedded tissue in bullous pemphigoid. Journal of Cutaneous Pathology. 2009;**36**(6):655-659

[9] Meijer JM, Diercks GF, Schmidt E, Pas HH, Jonkman MF. Laboratory diagnosis and clinical profile of anti-p200 Pemphigoid. JAMA Dermatol. 2016;**152**(8):897-904

[10] Vaughn Jones SA, Palmer I, Bhogal BS, Eady RA, Black MM. The use of Michel's transport medium for immunofluorescence and immunoelectron microscopy in autoimmune bullous diseases. Journal of Cutaneous Pathology. 1995;**22**(4):365-370

[11] Boraiy L, Fontao L. Michel's transport medium as an alternative to liquid nitrogen for PCR analysis of skin biopsy specimens. Dermatopathology (Basel). 2014;**1**(2):70-74

Chapter 8

Current Therapy in Autoimmune Bullous Diseases

Danka Svecova

Additional information is available at the end of the chapter

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Abstract

The goal of the treatment of autoimmune bullous disease is to reduce the production of pathogenic autoantibodies or increase elimination of pathogenic autoantibodies from serum of the patients. Immunosuppressive therapy reduces the production of autoantibodies. The therapy protocol is divided into three phases. The first is a control phase with the highest dose of immunosuppressive drugs suppressing activity of disease, followed with a consolidation phase, when the bulk of lesions is healed. The last phase is a maintenance phase when immunosuppressive medication is gradually tapered to the lowest level that suppresses the appearance of new lesions. In complete remission off therapy, the patient reached complete clinical remission and does not use any immunosuppressive medication. In complete remission on therapy, the patient uses a minimal immunosuppressive therapy. The first-line treatment is corticosteroids in pemphigus and pemphigoid groups. Adjuvant immunosuppressive drugs are combined with systemic corticosteroids and display a corticosteroid sparing effect. First-line immunosuppressive adjuvants comprise azathioprine, mycophenolate mofetil and mycophenolic acid. Rituximab, intravenous immunoglobulin G, immunoadsorption, cyclophosphamide, dapsone, and methotrexate are regarded as the second-line adjuvants. In dermatitis herpetiformis, a gluten free diet eliminates the clinical symptoms. Dapsone is regarded to be a valid therapeutic option in management of dermatitis herpetiformis.

Keywords: immunosuppressive therapy, corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, dapsone, rituximab, intravenous immunoglobulin G, immunoadsorption, tetracycline, gluten free diet

1. Introduction

Autoimmune bullous diseases belong to disorders that have low incidence but a high morbidity and mortality. Rupturing of blisters leads to painful erosions that cause significant loss of body fluid, electrolytes and proteins, especially in cases with extensive body surface involvement. If

mucous membrane of the mouth, pharynx and esophagus are involved, the patient may not be able to tolerate adequate intake of food and medication. Erosions on the skin and mucosa can lead to secondary infections which may cause life-threatening events such as sepsis and cardiac failure. Autoimmune bullous diseases warrant the use of high dose of systemic corticosteroids and immunosuppressive drugs that may be associated with various adverse and other side effects. Moreover, considerable risk for serious systemic complications should be predicted.

Pemphigus vulgaris is a rare autoimmune bullous disease, but one of the most severe with the highest morbidity and mortality rates, and one requiring the highest doses of corticosteroids and adjuvant agents. Before the advent of systemic corticosteroids, the prognosis of pemphigus vulgaris was fatal within 2 years from diagnosis. The introduction of corticosteroids in the 1950s dramatically reduced mortality rates from around 70 to 30%. The use of adjuvant immunosuppressive agent in management of autoimmune bullous diseases in the 1960s decreases mortality rates to 10% [1]. Nowadays, it is estimated that mortality rates of pemphigus is in the range of 5–10% [2]. Among autoimmune bullous disease, the most frequent disorder is bullous pemphigoid. The mortality rate of bullous pemphigoid is age dependent and ranges in 2.43–9.5% [3]. A higher mortality is influenced by old age, widespread disease, high dose of oral corticosteroids and life-threatening comorbidities. Bullous pemphigoid has shown increasing incidence rates in recent decades, especially in Western societies. However, bullous pemphigoid rarely represents a life-threatening disease. In bullous pemphigoid, the risk factors that can evoke disease should be identified and eradicated. A provoking drug or underlying malignancy is the most frequent risk factors in bullous pemphigoid. In therapy management, many immunosuppressive drugs are contraindicated because of comorbidities or malignancy in the history.

The therapy modalities used to treat autoimmune bullous disease have different mechanisms affecting the pathophysiology of the disease. Some medications yield in suppression production of the pathogenic autoantibodies and some have anti-inflammatory activity. Immunosuppressive activity is used in the corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, and others. Medication with anti-inflammatory activity is aimed at suppressing the inflammatory process. The last group includes topical corticosteroids, dapsone and sulfonamides, as well as anti-inflammatory antibiotics. Immunoadsorption is another modality using the removal of the pathogenic autoantibodies and inflammatory mediators. A new biologic therapy is intravenous immunoglobulin G and rituximab, monoclonal antibody to transmembrane protein CD20 of B-cells. In general, immunosuppressive and anti-inflammatory medications are commonly utilized in various autoimmune bullous diseases. Dermatitis herpetiformis is one of the diseases with specific treatment regimen, namely a gluten free diet that may improve gluten reverses of underlying gluten-sensitive enteropathy and so the results in remission of the skin disease.

2. Management of autoimmune bullous diseases

Management of autoimmune bullous disease should start with initial evaluation of the disease and the patient's condition in order to evaluate the risk of complications developing from immunosuppressive therapy. The clinical diagnosis should be confirmed with the histopathology of the blister, direct immunofluorescence microscopy (DIF) of the perilesional skin,

serological detection of autoantibodies by indirect immunofluorescence microscopy (IIF), enzyme-linked immunosorbent assay (ELISA), or immunoblot or immunoprecipitation.

The work-up before corticosteroid or immunosuppressive therapy should account for: a complete blood count, creatinine, urea, blood electrolytes, transaminases, gamma GT, alkaline phosphatase, total serum protein, albumin, glucose, hepatitis B, C and HIV, and chest X-ray. Optional examination predicting used medication includes analysis of thiopurine methyltransferase (TPMT) activity when azathioprine is considered; glucose-6-phosphate dehydrogenase (G6PD) serum activity, bilirubin, and reticulocytes if dapsone is recommended; and serum IgA deficiency should be ruled out prior to intravenous immunoglobulin therapy. Abdominal sonography is optional. QuantiFERONE or PPD is recommended where there is a risk of tuberculosis; a βhuman chorionic gonadotropin (βHCG) blood test is used to exclude pregnancy in women of childbearing age; osteodensitometry is recommended prior to corticosteroid therapy and periodically evaluated during the regimen; ophthalmological examination is performed prior to corticosteroid therapy and periodically repeated to exclude glaucoma and cataract.

A general examination should asses the patient's general condition including bodyweight, arterial blood pressure, and comorbidities such as cardiovascular, musculoskeletal or neoplastic, diabetes, etc.

Laboratory monitoring of pathogenic autoantibodies should be performed in autoimmune bullous diseases to predict outcome of the disease as well as to evaluate the efficacy of the employed therapy regimen.

In pemphigus patients, detection of pathogenic IgG antibodies by ELISA is positive in 90% of patients and correlates with disease activity. A quantitative evaluation of anti-Dsg3 and anti-Dsg1 IgG is evaluated using ELISA or IIF. Both methods can predict activity or curability of disorder. Determination of serum antibodies is performed on initiation of therapy, after 3 months and every 3–6 months based on disease activity and relapse [4]. Immunoblot and immunoprecipitation can also be used. In paraneoplastic pemphigus, the autoantibody to various antigens can be detected, including envoplakin, periplakin, desmocollin, desmoplakin, desmogleins, BP180 antigen, BP230 antigen, and plectin.

In patients with bullous pemphigoid, pathogenic anti-BP180 IgG autoantibodies are evaluated by ELISA or IIF. A quantitative evaluation should be monitored at days 0, 60, and 150 during treatment. A negative anti-BP180 IgG antibody at day 150 has a good predictive value of durable remission in approximately 90% [5].

In patients with dermatitis herpetiformis, pathogenic autoantibodies are IgA against tissue transglutaminase (anti-tTG) and IgA against endomysia (primate smooth muscle reticular connective tissue, EMA). Tissue transglutaminase (tTG) antigens share a 64% homology with epidermal transglutaminase, which is the target antigen in dermatitis herpetiformis. Detection by ELISA anti-tTG IgA is positive in 90% of patients with dermatitis herpetiformis. Detection of EMA IgA antibody uses IIF and is positive in 100% of patients with dermatitis herpetiformis [6]. Both markers are useful in detection of bowel damage and gluten-free diet compliance in patients with dermatitis herpetiformis and they disappear, if a gluten-free diet is strictly adherent. In general, monitoring of autoantibodies reflect patient's adherence to a gluten-free diet. Serological evaluation is sensitive to detecting major but not minor failure in diet.

Therapy protocol of pemphigus group diseases and pemphigoid diseases is divided into three phases, based on the activity of the disease. The first is the induction phase, followed by a consolidation phase and then a maintenance phase. During the induction phase, control of disease should be established usually by a high dose of immunosuppressant agent, mostly corticosteroids. Bullous disease usually responds to treatment within 2 weeks, provided the correct dose is used. In the consolidation phase, the dropped dose of medication is used until the bulk of lesions have been healed. Slow healing is an indicator that the dose of medication is inadequate and should be boosted. The maintenance phase begins once most lesions have been healed (80%). The rate of medication tapering is based on clinical improvement of the disease and the physician's experience. If new lesions (one to five) appear while medication is tapering, these can be treated with high potency topical or intralesional corticosteroid, while maintaining patients on their current dose of systemic medications. If many new lesions appear, the dose of corticosteroids should be increased in 25–50% increments until control of disease is achieved. In most patients, the healing is slow, often requiring a period of 1–3 months for complete clearance of lesions. Discontinuation of immunosuppressive therapy may be proposed if complete remission is achieved with a low dose of systemic corticosteroid (prednisolone ≤10 mg/day) for a period of 6–12 months. Remission should be supported by negative DIF data. DIF data is a sensitive method for autoantibody detection in tissue in active disease, as well as in remission. Furthermore, DIF data correlate with the immunological activity of the disease. Patients with a higher autoantibody titer and positive DIF data are likely to experience disease relapse. In pemphigus group, the titer of autoantibodies correlates with disease activity, while not so closely in the bullous pemphigoid group, but also is used in monitoring.

The aim of treatment is to suppress disease activity with the minimum dose of drug necessary to induce complete remission, with minimum dose resulting in minimum adverse events, allowing all therapies to be discontinued. Duration of different treatment regimens is not standardized, ranging from 1 to 5 years or even longer. Long-term treatment leads to a high accumulation of corticosteroids and adjuvant drugs, leading to the development of adverse events from all used medications. In general, minimizing potential adverse effects of corticosteroids could be managed by agent that reduces osteoporosis and antacids, following a diet low in sugar and salt. In methotrexate protocol, the bone marrow depression could be reduced with folic acid. It is also important to reduce risk factors such as bacterial or viral infections, sun exposure and radiation therapy, large dental procedure, and psychical stress. In dermatitis herpetiformis, the most preferred precaution is to avoid a diet failure. Physicians and patients should be aware that autoimmune bullous diseases may not require lifelong treatment. However, patients with autoimmune bullous diseases should be monitored in their clinical remission and blood analysis for autoantibody detection. Both help to evaluate the risk of disease flaring up.

3. Systemic treatment of pemphigus group

3.1. Systemic induction therapy

Systemic induction therapy should be started with systemic immunosuppressive medication in combination with topical antiseptic agents and possible topical corticosteroids. Only in

exceptional cases of limited disease and minor severity, monotherapy with topical corticosteroids or with topical calcineurin inhibitors may be considered. However, patient clinical symptoms and the presence of autoantibody level should be evaluated.

Corticosteroids are the mainstay therapy in management of mild to severe disease of all subtypes of pemphigus due to their rapid effects, resulting in a significant improvement in morbidity and mortality rates. Corticosteroids are regarded as a first-line treatment for initial management of pemphigus. Prednisolone equivalent of 0.5–1.5 mg/kg/day is recommended as the initial dose in induction therapy, depending on disease severity, patient age, and comorbidities. To control pemphigus foliaceus, generally, lower doses than that of pemphigus vulgaris are required. If the control of the disease is not achieved within 2 weeks, a higher prednisolone equivalent up to 2.0 mg/kg/day is optional. In severe and recalcitrant disease, a daily dose above 100 mg should be utilized intravenously in pulse therapy mode. Doses of pulse therapy are not standardized. Methylprednisolone 10–20 mg/kg/day (250–1000 mg) is administered every day on 3 consecutive days in intervals of 3–4 weeks, subsequently for 6–8 weeks [7]. Another choice is to use dexamethasone 2–5 mg/kg (50–200 mg). The aim of pulsing is to achieve more rapid and effective disease control compared with conventional oral dosing. However, adverse effects are common and dose related. The dosing schedule is advocated according to disease severity. Patients with mild disease are treated with initial prednisolone equivalent 40–60 mg/day, and more severe cases with 60–100 mg/day. If the patient does not respond within 5–7 days, the dose should be increased in 50–100% increments until disease control is achieved. When a patient does not respond well to systemic prednisolone therapy even at higher doses, the change of prednisolone to other oral corticosteroid (e.g., betamethasone, dexamethasone or methylprednisolone) might improve patient's condition [8]. Autoantibody titers fall with clinical healing, but the decrease of autoantibody titer is slower than clinical improvement.

Systemic corticosteroids can be combined with an immunosuppressive adjuvant agent at the start of therapy, especially in individuals with increased risk of corticosteroid-related side effects (**Table 1**). However, the addition of an adjuvant agent in induction therapy was not exactly confirmed and documented. Adjuvant drugs are usually administered in combination with a systemic corticosteroid to reduce related adverse and side effects and increase the immunosuppressive efficacy of medication. Their corticosteroid-sparing effect may lead to corticosteroid-free remission. If an adjuvant agent is utilized at the induction phase of treatment combined with corticosteroid, its efficacy should be expected in within approximately 1 month, depending on the specific adjuvant drug. Some authorities believe that the time to induce remission is shorter in high dose oral prednisolone monotherapy than with low dose oral prednisolone combined with an adjuvant drug. Moreover, rapidly progressive lesions necessitate a high dose of corticosteroid for early and adequate control of the disease. However, the significantly higher dose directly correlates to increased rates of treatment-associated adverse events. Therapy-related side and adverse effects and complications should be expected in prolonged administration of more than 4 months or at prednisolone dose ≥10 mg/day [1].

In severe and refractory cases, the induction therapy can be started with second-line adjuvant agents' rituximab, intravenous immunoglobulins or by immunoadsorption.

First-line therapy	Dose initial therapy
Prednisolone	0.5–1.5 mg/kg/day
Second-line therapy (first-line adjuvant agent)	
Azathioprine	1–3 mg/kg/day
Mycophenolate mofetil	2 g/day
Mycophenolic acid	1440 mg/day
Third-line therapy (second-line adjuvant agent)	
Cyclophosphamide	500 m i.v. bolus or 2 mg/kg/day orally
Methotrexate	10–20 mg/week
Dapsone	100 mg/day or up to ≤1.5 mg/kg/day
Anti-CD20 monoclonal antibody (rituximab)	2×1 g i.v. (2 weeks apart) or 4×375 mg/m^2 (each 1 week apart)
Intravenous immunoglobulin G	2 g/kg/4 weeks i.v.
Immunoadsorption	2 cycles a 4 days, 4 weeks apart
Pemphigus herpetiformis	
Dapsone + prednisolone	100–300 mg/day + low dose of prednisolone
IgA pemphigus	
Dapsone + prednisolone	100–300 mg/day + low dose of prednisolone
Acitretin	50 mg/day

First-line therapy uses systemic corticosteroid that has rapid immunosuppressive efficacy. Second-line therapy is used in refractory disease or in contraindications to systemic corticosteroids. First-line adjuvant agents have corticosteroid-sparing effect. Second-line adjuvant agents are used in refractory disease or in contraindications to first-line adjuvant agents.

Table 1. Systemic treatment of pemphigus group.

3.2. Systemic consolidation therapy

Systemic consolidation therapy in pemphigus vulgaris starts as soon as control of disease activity is achieved and approximately 80% of lesions are healed. Tapering of the corticosteroid can start by approximately 25% of the dose at 7–14-days intervals. If tapering reached a prednisolone equivalent of 20 mg/day, slower tapering at 2- to 4-week intervals is recommended. If relapse of the disease develops in the consolidation phase, systemic corticosteroid dose should be returned to two reduction intervals before. If control of disease activity is achieved within 14 days, tapering of corticosteroid can continue. If control of disease activity is not achieved, it is recommended to return to the initial systemic corticosteroid dose [1, 7].

Immunosuppressive efficacy of systemic corticosteroid is enhanced, if combination with other immunosuppressive adjuvant is used, including azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate or dapsone. Most adjuvant immunosuppressive drugs act more slowly than corticosteroids and their efficacy manifests within several weeks. Therefore, adjuvant agents are most frequently utilized after control of disease activity is achieved.

3.3. Systemic maintenance therapy

In the systemic maintenance phase, systemic corticosteroid is gradually tapering to the lowest level that suppresses the appearance of new lesions, with the goal being to discontinue all medications eventually. If a patient is treated with two or more immunosuppressive drugs, these should be tapered one at a time. Corticosteroid tapering continues from the consolidation phase and other immunosuppressive agents should be tapered later. Tapering too rapidly increases the chance of relapse, while tapering too slowly may lead to medication-related side effects. In complete remission on therapy, the patient receives minimal therapy, i.e., less than 10 mg/day prednisolone and/or minimal adjuvant therapy for at least 2 months. Minimal adjuvant therapy is defined as half of the initial dose. The systemic corticosteroid dose is reduced by approximately 25% at 7 to 14 days and gradual conversion to an alternate day schedule once the daily dose is at 10–8 mg. The rate of medication tapering is based on the clinical outcome and physician's experience. If autoantibody does not continue to fall and new lesions (one to three) appear while medication is being tapered, new lesions could be treated with intralesional or highly potent topical corticosteroid while maintaining the patients on their current dose of systemic medications [9]. The appearance of three to five lesions in a month that do not heal spontaneously within 1 week is regarded to be a relapse of disease in the maintenance phase. The dose of medication should be returned to the dose given two reduction intervals before until control of the disease is achieved.

Remission on minimal maintenance dose, negative autoantibody level, and negative DIF data are indicating markers for discontinuation of immunosuppressive medication. It is recommended to control the DIF data, if the patient is on a minimal maintenance dose for about 6–12 months with total clinical clearance [1]. Healthy skin from the sacral area not irradiated by the sun and covered with suits is a suitable sample for DIF. In addition, discontinuation of medication can ultimately be compassed in most patients. The proportion of patients in whom discontinuation of immunosuppressive therapy can be achieved increases steadily with time, and it can be discontinued in approximately 50% of patients after 3 years and in 75% of patients after 10 years [10, 11].

Prolonged treatment lead to high cumulative doses of corticosteroids and adjuvant drugs and medication-related side and adverse effects.

3.4. Adjuvant drugs

The application of adjuvant drugs into the therapy regimen of autoimmune bullous skin disorders allows the period of high dose corticosteroids application to be shortened. Adjuvant drugs have a corticosteroid-sparing effect, following with a decrease of corticosteroid-related side and adverse effects and an increase in the immunosuppressive efficacy of the regimen. Recently, several adjuvant agents have been utilized as an initial treatment in combination with corticosteroids.

3.4.1. Azathioprine

Among adjuvant agents, azathioprine is regarded as a first-line adjuvant with corticosteroid-sparing efficacy, most frequently used to treat autoimmune bullous disease including

pemphigus. Azathioprine is a purine analog with specific activity to lymphocytes and is more selective for T-cells than B-cells [12]. Azathioprine interferes with purine synthesis and metabolism, leading to delayed action of drug, as it usually takes at least 1–2 months [13].

Extensive experience with azathioprine refers to good efficacy, tolerability and safety profiles. One study compared four regimens in 120 patients with pemphigus vulgaris. The efficacy of prednisolone was enhanced, when the drug was combined with an immunosuppressive adjuvant. Among adjuvants, azathioprine showed the highest corticosteroid-sparing effect. Other compared adjuvants were mycophenolate mofetil, intravenous cyclophosphamide, and prednisolone alone. In general, azathioprine is believed to be more effective than corticosteroid alone, both in terms of mortality and morbidity rates [14]. Another review evaluated 20 clinical studies comprehending data of 826 patients with pemphigus vulgaris and pemphigus foliaceus and confirmed the very good corticosteroid-sparing effect of azathioprine better than cyclophosphamide. However, azathioprine did not increase the remission rate [15]. The next review evaluated 10 clinical studies that comprehended data of 559 participants treated with various adjuvants, including azathioprine, mycophenolate mofetil, cyclophosphamide, intravenous immunoglobulins, plasma exchange and infliximab. All adjuvants collectively decreased the risk of relapse by 29%, but all of them did not increase the remission rate [16]. The corticosteroid-sparing effect of azathioprine was also confirmed in a review study of 11 studies with 404 participants [17].

The activity of thiopurine methyltransferase (TPMT) should be evaluated before the beginning of therapy with azathioprine. Decreased activity of TPMT takes place in induction of an adverse event. In the Japanese population, an adverse event of azathioprine was associated with gene mutation of inosine triphosphate pyrophosphohydrolase (ITPA), another enzyme metabolizing azathioprine [18]. It is recommended to start therapy with a low initial dose of azathioprine 50 mg/day to detect idiosyncratic reactions. If the activity of TPMT shows normal levels, the dose can be increased to 1–3 mg/kg/day depending on the clinical outcome. If TPMT activity shows an intermediate or low level, it should be applied in a lower dose up to 0.5–1.5 mg/kg/day. Patients with insufficiency of TMPT activity are at risk and should not be treated with azathioprine because they may experience rapid bone marrow suppression after initiation of therapy. Furthermore, some patients may experience complications despite normal TPMT activity. All patients at risk of severe toxicity should undergo close monitoring of clinical and hematologic parameters, including liver enzyme levels. Likewise, an abrupt increase in liver enzymes observed soon after administration of azathioprine is a clue to deficient TPMT activity. In addition, concurrent therapy with TPMT-inhibiting drugs, such as allopurinol or sulfasalazine, can also increase the risk of myelotoxicity [19].

If the clinical outcome improves, the lowest effective dosage should be administered. If no improvement occurs within 3 months, the drug should be withdrawn and changed for another adjuvant agent. However, in patients who achieve improvement in clinical outcome, care should be taken in monitoring for myelosuppression and hepatotoxicity. It is strictly recommended to monitor the full blood count weekly over a period of 8 weeks, then at a minimum of once every 3 months. In addition, liver functions should be monitored.

Adverse drug reactions with azathioprine occur in 15–30% of patients and include leucopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity [13]. Long-lasting immunosuppression

increases the risk of infections and only a minor increase of neoplasia, mostly lymphoma [20]. In addition, alopecia, rash or gastrointestinal disturbances (nausea, vomiting, anorexia, diarrhea, aphthous stomatitis, and pancreatitis) can be observed. In pregnancy and breastfeeding, azathioprine is contraindicated due to the risk to the child [21].

Extensive experience with azathioprine refers to good efficacy and safety profile and the drug is recommended as a first-line adjuvant agent with corticosteroid-sparing immunosuppressive in the second line of treatment in moderate to severe pemphigus vulgaris and pemphigus foliaceus, and other types of pemphigus.

3.4.2. Mycophenolate mofetil and mycophenolic acid

Mycophenolate mofetil is an esterified prodrug of mycophenolic acid. Both belong to first-line adjuvants. Mycophenolic acid is an active metabolite that selectively inhibits inosine monophosphate dehydrogenase, an enzyme involved in *de novo* synthesis of quanosine nucleotides. Mycophenolate mofetil inhibits T-cells and B-cells proliferation, and antibody production by B-cells [22]. The induction of disease remission often requires at least 8 weeks of treatment.

One study compared combined therapy of corticosteroid with mycophenolate mofetil or azathioprine. Both adjuvants demonstrated similar efficacy, sparing effect, and safety profiles [23]. Very good efficacy was demonstrated in 18 patients with pemphigus vulgaris treated with mycophenolate mofetil using a conventional dose, with 89% of them achieving complete disease control. The average time to achieve 75% clearance of lesions was 4.5 months. Three patients discontinued all immunosuppressive therapy, including mycophenolate mofetil, in an average of 3 years [24]. Another review of 11 clinical studies comprehended data of 404 patients with pemphigus vulgaris and pemphigus foliaceus and evaluated mycophenolate mofetil as more effective in achieving disease control than azathioprine [17]. Mycophenolate mofetil is regarded to be less myelosuppressive and hepatotoxic than azathioprine [20].

Adverse drug reactions include especially gastrointestinal events such as diarrhea, nausea, vomiting, following with infections, leucopenia, and anemia. Hematologic findings are dose-related and reversible. In general, mycophenolate mofetil is well-tolerated and serious adverse effects are rarely observed. The recommended dose of mycophenolate mofetil is 0.5–2 g/day or mycophenolic acid at 1440 mg/day. However, increasing the daily dose by 1 capsule (500 mg) per week is recommended until the final dose of 2 g/day to evoke better gastrointestinal tolerance. Enteric-coated mycophenolate sodium was prepared to minimize gastrointestinal side effects and improve quality-of-life and compliance to treatment [25]. Mycophenolate mofetil is contraindicated in pregnancy because of the increased risk of miscarriage and congenital malformations [21]. Mizoribine is a newly developed immunosuppressive agent affecting purine synthesis similar to mycophenolate mofetil and can be utilized in patients with autoimmune bullous diseases, including pemphigus vulgaris [26]. It is suspected that mizoribine would have lower toxicity and higher tolerability than other immunosuppressants, such as azathioprine or cyclosporine.

Mycophenolate mofetil displayed a very good safety and efficacy profile as a first-line adjuvant agent and could replace azathioprine as an antimetabolite adjuvant of choice in the

second-line treatment of many autoimmune and inflammatory diseases, including moderate to severe pemphigus vulgaris and pemphigus foliaceus as well as other types of pemphigus.

3.4.3. Cyclophosphamide

Cyclophosphamide is a second-line adjuvant agent that can be utilized when first-line adjuvant agents fail to evoke remission or a corticosteroid-sparing effect. Cyclophosphamide is an alkylating agent with highly effective immunosuppressive activity. It alkylates DNA at various positions, resulting in cell cycle arrest, DNA repair, and apoptosis. Proliferating tissues with a high mitotic rate are the most susceptible to cyclophosphamide. However, its activity is not cell cycle-dependent. Both cellular and humoral immunity is suppressed [27]. The toxicity is significantly higher than that of azathioprine and therefore it is reserved for the most severe and refractory diseases.

Several studies demonstrated that oral cyclophosphamide is an effective adjuvant in the treatment of severe and refractory pemphigus vulgaris and pemphigus foliaceus in dose 2–2.5 mg/kg/day each morning followed by massive oral hydration of at least 2–3 L of fluids [28]. One retrospective study evaluated therapy in 101 patients with pemphigus vulgaris. Authors compared oral cyclophosphamide, azathioprine, and cyclosporine. Cyclophosphamide was evaluated as the drug with the best remission and relapse rates [29]. Another comparative study of 16 patients with pemphigus vulgaris showed a faster onset of activity in cyclophosphamide than azathioprine, but the evaluation of efficacy in both did not differ [30]. One prospective study of 11 patients with pemphigus compared dexamethasone-cyclophosphamide pulse therapy with oral corticosteroid (methylprednisolone)-azathioprine therapy in conventional doses and failed to find significant benefits between these two regimens, besides fewer recurrences in pulse therapy with cyclophosphamide [31]. Cyclophosphamide showed a very good corticosteroid-sparing effect [29].

Several dosing schedules have been developed to minimize cumulative dose and susceptibility to adverse events. These include monthly intravenous administration (500 mg) in conjugation with low oral dose daily between infusions (2.0 mg/kg/day). A single dose of intravenous immunoablative therapy can also be used. However, daily oral cyclophosphamide results in the highest cumulative dose. On the other hand, continuous daily exposure provides optimal immunosuppression. In severe recalcitrant pemphigus vulgaris, a combined regimen of pulsed intravenous cyclophosphamide with corticosteroid could be used. The pulse regimen consists of the intermittent administration of a high dose of corticosteroid and cyclophosphamide, usually as three daily doses of corticosteroid (dexamethasone 100 mg or methylprednisolone 500–1000 mg) and a single dose of cyclophosphamide (500 mg). Such corticosteroid-cyclophosphamide pulses can be administered once a month over a period of several months. Between these pulses, the patient receives cyclophosphamide 2 mg/kg/day.

In cyclophosphamide therapy, adverse events are frequent, including hemorrhagic cystitis and high susceptibility to infection. Mutagenic activity increases an individual's lifetime risk for transitional cell carcinoma of the bladder and hematologic malignancies. This risk is proportional to the cumulative dose of the drug. Moreover, acute myelosuppression can be developed in 6–10 days and recovered in 14–21 days after discontinuation of cyclophosphamide.

However, another adverse gastrointestinal event may develop, including mucosal ulcers, nausea, vomiting, stomach pain, and diarrhea. Potential gonadal toxicity is associated with amenorrhea, azoospermia, and infertility [19]. In addition, cardiotoxicity, hepatotoxicity, interstitial lung fibrosis, darkening of the skin and nails, alopecia, changes to hair color and texture, and lethargy may develop.

The efficacy and safety profile raised cyclophosphamide as a second-line adjuvant drug of choice in the third line of treatment in severe and refractory pemphigus vulgaris and pemphigus foliaceus.

3.4.4. Methotrexate

Methotrexate was primarily developed to treat malignancies. Recently, methotrexate has been used as an immunosuppressive and anti-inflammatory agent. Methotrexate is a folate antagonist that competitively inhibits dihydrofolate reductase, resulting in blocking of several folate-dependent enzymes integral to DNA synthesis. The synthesis of purine and pyrimidine nucleotides is involved, which in turn is necessary for synthesis of DNA and RNA. The drug affects the S-phase of the cell cycle, thus inhibiting rapidly proliferating cells, including malignant, hematopoietic, and mucosal [32]. However, methotrexate inhibits cell proliferation especially at higher doses. At lower doses, the drug has anti-inflammatory activity. The mechanism of anti-inflammatory activity is not fully understood. It could be mediated via a pathway separate from folate antagonism. The drug may evoke the inhibition of polyamines, resulting in a net increase in intracellular and extracellular adenosine. Adenosine is a purine nucleoside with potent anti-inflammatory effect on many different target cells [32, 33].

Methotrexate was the first adjuvant drug to be combined with corticosteroid in the management of autoimmune bullous diseases. A retrospective analysis of 7 clinical studies evaluated the efficacy of methotrexate in 116 patients with pemphigus vulgaris. Of those, 83% showed clinical improvement. Fourteen patients achieved total remission and were off therapy by a mean of 2.6 years after discontinuation of methotrexate and systemic corticosteroid. Nausea and infection were the most frequent side effects and one patient died due to bronchopneumonia [34].

At present, a methotrexate dose of 10–20 mg/week is used orally to treat autoimmune bullous diseases, including pemphigus vulgaris. A test dose of 2.5–5 mg is recommended at the initiation of therapy. If the drug is tolerated, the dose can be escalated to the therapeutic dose. Methotrexate has good oral bioavailability and is akin to parenteral administration. However, interindividual absorption variability exists. Therefore, in patients with an inadequate answer to oral administration, a switch to intramuscular dosing is recommended. Folic acid is used to decrease the deleterious side effects of methotrexate and can be used the next day in a dose of 1–5 mg or daily. Folic acid supplementation can prevent folate deficiency, improving tolerance and preventing anemia, neutropenia, stomatitis, and oral ulcers. Methotrexate is a corticosteroid-sparing agent with delayed, beneficial effect on oral lesions, whereas the cutaneous lesions usually respond very well and rapidly. Methotrexate may interact with nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, sulfasalazine and phenytoin, resulting in increased time to eliminate methotrexate. These interactions may result in severe bone marrow toxicity. Adverse events

involving methotrexate are usually mild and self-limiting or preventable. When an adverse event occurs, the dosage should be decreased or withdrawn. In a relatively brief time, the adverse effects may consolidate in a normal condition. The most frequent adverse effects include nausea, anorexia, vomiting, diarrhea, fatigue, and malaise. Fatigue and nausea may be minimized by taking the drug before bedtime and by folic acid supplementation. In general, adverse effects are dose-dependent and usually appear around the initiation of therapy. A serious adverse event is myelosuppression, which can develop in patients with potential risk factors like renal insufficiency, senescence, concomitant serious illness or infection, drug overdose or drug interaction. In severe cases, myelosuppression is considered a potentially fatal condition, but usually improves after dose reduction or withdrawal. Mucositis is regarded as precursor of developing pancytopenia, and should be taken seriously. Patients with significant pancytopenia (WB ≤ 3000, Hg ≤ 11, platelets ≤ 50,000) should be treated immediately with intravenous leucovorin (folinic acid), the antidote to methotrexate, that is able to bypass dihydrofolate reductase [35]. In addition, hepatotoxicity, resulting in fibrosis and cirrhosis, is a serious adverse event associated with long-term administration of methotrexate, when the cumulative dose reached 9.5–26 g [34]. Obesity, diabetes mellitus and excessive alcohol consumption are regarded as risk factors for liver toxicity. According to the Manchester protocol, serum procollagen III aminopeptide (PIIINP) assay may be used to monitor liver toxicity resulting from methotrexate toxicity [36]. If PIIINP assay is not approachable, some authors predict a liver biopsy. A liver biopsy is recommended when the total cumulative dose reaches 3.5–4.0 g [37]. Monitoring of liver function and bone marrow is recommended to be repeated regularly to avoid myelosuppression and hepatotoxicity. Methotrexate is contraindicated in pregnancy due to its teratogenic and abortifacient properties. Moreover, it causes reproductive toxicity and decreases the sperm account [38]. Mucocutaneous toxicity occurs more commonly in patients without adequate folic acid supplementation. In severe cases, it can be associated with diarrhea and myelosuppression. Mucocutaneous toxicity can start with mucositis or very painful oral ulceration. More rarely, ulceration of the skin could be an early harbinger of methotrexate toxicity.

Methotrexate is a corticosteroid sparing agent and is recommended as a second-line adjuvant in the third-line treatment of moderate to severe pemphigus vulgaris and pemphigus foliaceus. The drug is relatively inexpensive.

3.4.5. Dapsone

Dapsone is a sulfone-derived drug that primarily possesses both antimicrobial and antiprotozoal activities. Additionally, dapsone has anti-inflammatory properties like non-steroidal anti-inflammatory drugs. Dapsone suppresses neutrophilic infiltration by inhibition of neutrophil activation and recruitment through many different pathways [39].

One multicenter randomized, double blind study confirmed the glucocorticoid-sparing efficacy of dapsone in 19 patients with pemphigus vulgaris. Seventy-three percent of patients treated with dapsone achieved remission [40]. A retrospective review study analyzed 35 case series and case reports comprehending data of 427 patients with autoimmune bullous disease. Among them were 55 patients with pemphigus (32 patients with pemphigus vulgaris and 14 with pemphigus foliaceus). Dapsone was evaluated as an effective and useful corticosteroid-sparing

agent in therapy of autoimmune bullous disease, including pemphigus. Adverse events were dose-dependent and reversible. The most frequent adverse event was hemolysis and concomitant anemia secondary to hemolysis [41].

The recommended dose of dapsone is 100 mg/day or up to ≤1.5 mg/kg/day. Prior to start dapsone therapy, glucose-6-phosphate dehydrogenase deficiency should be excluded, and cell blood counts, renal and liver functions must be examined. During dapsone therapy, cell blood counts including reticulocyte, leukocyte and platelet, and the level of methemoglobin, should be regularly monitored. It is recommended to start dapsone therapy with a low dose of 0.5 mg/kg/day. If the drug is tolerated, the dose can escalate slowly up to the effective dose [39]. A rapid enhancement of medication may result in a severe hemolytic anemia. Adverse events are dose-dependent and transient. However, frequent adverse effects include hemolytic anemia and methemoglobinemia which may necessitate halting treatment. A high dose of vitamin C supplementation can evoke better tolerability of dapsone, including a drop in the methemoglobin level. In addition, headache is a common adverse event. More serious complications are hepatitis, hypersensitivity syndrome and agranulocytosis. Peripheral neuropathy is a rare adverse event and may involve both motor and sensory nerves [39]. Most complications are referred in the first 3 months of treatment. Precaution should by mentioned in the second trimester of pregnancy, when dapsone should be reduced or stopped. If dapsone is not tolerated, it could be replaced with other sulfonamides, e.g., sulfapyridine (1.5 g/day) or sulfamethoxypyridazine (0.25–1.5 g/day). In addition, sulfonamides are contraindicated in breastfeeding women because they may induce hemolytic anemia in an infant.

Dapsone is recommended as a second-line adjuvant agent to treat mild to severe pemphigus vulgaris and pemphigus foliaceus, especially in the maintenance phase of their management. The drug is a corticosteroid-sparing agent recommended with either low or intermediate doses of systemic corticosteroid and may allow tapering or discontinuation of corticosteroid doses. Dapsone is regarded as a third-line therapy in pemphigus diseases.

3.4.6. Anti-CD20 monoclonal antibody (rituximab)

Rituximab is a murine/human chimeric monoclonal antibody, targeting the CD20 molecule found on the cell surface of B-cells of various maturate stages up to the preplasma cell stage. Stem cells or B-cell progenitors, plasmablasts, and plasma cells, do not express the CD20 molecule and do not respond to rituximab. Among several mechanisms involved in pathophysiology of autoimmune bullous disease, rituximab exerts B-cell cytotoxic activity mainly through antibody-dependent cell-mediated cytotoxicity, resulting in depletion of B-cells that presumably produce pathogenic antibodies. Depletion of B-cells persists in circulation for 6–12 months. However, after the rituximab treatment, the B-cell count returns to normal levels. Even so, replacement of B-cells is not associated with relapse in a considerable number of patients with autoimmune disease. These data suggest that rituximab-mediated depletion of B-cells may influence also other cells participating in immune tolerance and homeostasis. In addition, the depletion of B-cells may participate in decreasing resistance against infection. One study demonstrated a significant reduction of T regulatory cells after rituximab therapy. This event may be due to increased skin homing of these cells [42].

Primarily, rituximab was used for treating non-Hodgkin's B-cell lymphoma. The use of rituximab in pemphigus began after a marked improvement in lymphoma-associated paraneoplastic pemphigus [43]. Rituximab has a late onset of action to control acute disease and produces an initial clinical response in 69 weeks or less. It should therefore, be used as an adjuvant agent combined with systemic corticosteroids and/or another adjuvant agent. Two FDA protocols for rituximab management can be used to treat autoimmune bullous disease, including pemphigus. The lymphoma protocol utilizes four infusions of rituximab 375 mg/m^2 given in four consecutive weeks, a week apart. The rheumatoid arthritis protocol uses two infusions at a dose of 1 g, given 2 weeks apart. Even though both protocols are effective, the rheumatoid arthritis protocol could prove better because both rheumatoid arthritis and pemphigus are autoimmune diseases. One retrospective review report evaluated 42 clinical studies comprehending data of 272 patients with pemphigus vulgaris who have been treated with rituximab. Data of the review study showed that a complete remission was achieved in 66.6% of patients on the lymphoma protocol and 75% on the rheumatoid arthritis protocol within an 18-month follow-up. During this period, 11.1% of patients treated with the lymphoma protocol achieved remission and were off therapy and 33.3% on minimal immunosuppressive therapy. Meanwhile, on the rheumatoid arthritis protocol, 53.3% of patients achieved remission off therapy and 17.4% on minimal immunosuppressive therapy. A partial response was observed in 12.8% of patients on the lymphoma protocol, and in 23.9% of patients on the rheumatoid arthritis protocol. The relapse rates were 22.8% on the lymphoma protocol and 35.9% on the rheumatoid arthritis protocol. The incidence of serious infections was 3.9% on the lymphoma protocol and 15.2% on the rheumatoid arthritis protocol. The mortality rate on the lymphoma protocol was 2.2% and 1.1% on the rheumatoid arthritis protocol [44]. Remarkable differences were observed in patient's response between both protocols. At present, the reason for protocol differences cannot be detected. Rituximab has a corticosteroid-sparing effect. In the future, a modified protocol for autoimmune bullous disease should be designed and evaluated. Some patients can develop resistance and do not respond to the rituximab regimen. The resistance can be due to the autoantibody to rituximab that interferes with drug binding or the pharmacokinetics of the drug could be changed by other ways.

Intravenous administration of rituximab should be initiated with premedication before each infusion using an antipyretic, e.g., paracetamol 1000 mg orally, or antihistamine. Prior to the first infusion, prednisolone 100 mg orally is advised. Rituximab infusion should be administered over 4–5 h. One cycle of rituximab may be repeated. Pathological lesions start to heal within just a few weeks after the first rituximab infusion and maximal effect can be expected after 3–4 months. Remission rates after the first-treatment cycle reached 76%. Repeating treatment further increased the remission rates to 91% [45].

Rituximab is generally well tolerated, and serious adverse effects are rare. Infusion-related reactions include anaphylaxis, hypotension, fever, chills, headache, weakness, nausea, pruritus and rash. Infusion-related reactions could be ameliorated by premedication before each infusion, then by decelerating or temporarily stopping of infusion. In addition, deep venous thrombosis of the lower limb and pulmonary embolism are serious complications. A frequent adverse event is the infection afflicting around 30% of patients, with a larger account of bacterial than viral infections. Moreover, herpes zoster is reported in several cases. Higher rates of infection could be influenced by concomitant treatment with an immunosuppressive agent, including corticosteroids. Another

serious adverse event may accompany rituximab treatment like *Pneumocystis carinii* infection causing pneumonia or septic shock, which may cause death.

In addition, rituximab is an effective drug in controlling recalcitrant disease and is recommended as the second-line adjuvant to treat severe refractory autoimmune bullous diseases, including pemphigus vulgaris, pemphigus foliaceus and pemphigus paraneoplastic. Complications such as fatal infections and other serious adverse events place the drug to the last resort treatment restricted for severe and refractory cases. Rituximab is recommended when other second-line adjuvant agents, including immunoadsorption and intravenous immunoglobulins, fail in the treatment or patients have multiple relapses. Despite the threat of serious adverse events, several reports would like to recommend rituximab as a first-line treatment accompanied with low dose of corticosteroids in patients with moderate to severe pemphigus [46]. The regimen proved effective and caused fewer adverse events than the regimen using corticosteroids alone [47]. First-line treatment with rituximab should be regarded in pemphigus patients, who are contraindicated to corticosteroid and other immunosuppressive therapy [47–49]. In near future, a new protocol for pemphigus patients should be elaborated and confirmed in clinical trials. Another study recommended rituximab combined with intravenous immunoglobulins as a first-line therapy in severe and refractory pemphigus. This regimen can evoke prolonged remission and could be used when corticosteroids and immunosuppressive adjuvants are contraindicated [50].

Research into biologic agents discovered new molecules that could be used in the management of autoimmune bullous diseases. New humanized anti-CD20 monoclonal antibodies modify or bind to different sites to the target molecules. The new molecules escalate activity and possess a higher efficacy in preclinical trials. All of them are of second or third generations of humanized anti-CD20 monoclonal antibody. Furthermore, efficacy, safety, and tolerability should be evaluated in clinical trials. Among them, veltuzumab is an anti-CD20 monoclonal antibody that is largely identical to rituximab. Its advantage is subcutaneous administration. Obinutuzumab possesses 50-fold greater binding and stronger induction of apoptosis than rituximab resulting in a rapid and profound B-cell depletion during the first infusion. Ofatumumab possesses a superior and longer-lasting cytotoxic effect than rituximab. It is used intravenously. Ocaratuzumab has a higher binding affinity and 10-fold higher cytotoxicity, which results in smaller dosage using subcutaneous administration. PRO131921 has 30-fold higher binding affinity and 10-fold higher cytotoxicity than rituximab. It is used intravenously [51]. New humanized anti-CD20 monoclonal antibodies require further clinical trials to evaluate and establish dosing, efficacy and safety, including the monitoring of potential adverse events.

According to the guidelines rituximab is recommended as a second-line adjuvant for severe and refractory pemphigus vulgaris. Rituximab can be utilized, when the failure of conventional therapy is present, e.g., severe adverse events in conventional therapy, contraindications to use a high dose of other immunosuppressive therapies and progressive and rapid uncontrolled disease. Rituximab is regarded as a third-line therapy in pemphigus diseases.

3.4.7. Intravenous immunoglobulin G

Primarily, high intravenous immunoglobulin G was used to treat primary immunodeficiencies, immune thrombocytopenic purpura, Kawasaki disease, chronic B-cell lymphocytic leukemia,

pediatric AIDS and others. In recent years, intravenous immunoglobulin has been used in the treatment of autoimmune and chronic inflammatory diseases, including autoimmune bullous diseases.

Immunoglobulin preparations are a special type of biologic treatment obtained from the pooled plasma of multiple healthy donors amounting 3000–10,000. Purified, pooled plasma contains natural antibodies of the IgG subclass. Natural autoantibodies are believed to play a role in maintaining immune homeostasis. Moreover, it contains a repertoire of the all IgG antibodies from populations as a mirror of the interaction of intravenous immunoglobulin individuals with external pathogens. Plasma may contain also natural autoantibodies, which presents the risk of preparation, but a considerable number of donors assists in dilution of these molecules. In addition, pooled plasma may contain a minimal refused amount of IgA or IgM. The guidelines for processing plasma are precise and stringent to avoid especially viral and bacterial contaminations. For this reason, pooled plasma is stored for 60 days and donors are checked for seroconversation to several pathogens. Individual plasma is also examined by polymerase chain reaction (PCR) for the presence of HCV RNA, HBV DNA, HIV RNA, HAV RNA and Parvovirus B19 DNA [52]. Only plasma with no pathogens may be collected to the pool preparation. Pulled plasma is evaluated for the main biological and pharmacological properties, the degree of purity and the antibody spectrum. The half-life of intravenous immunoglobulin is approximately 3 weeks.

The mechanism of intravenous immunoglobulin assesses several activities involving in activity complex. The desired response of intravenous immunoglobulin is a rapid decline in pathogenic autoantibodies and improvement of disease. The intravenous immunoglobulin produces complement blockade and degradation, Fc-receptor blockade and induces immunomodulatory Fc receptors, inhibits B-cells, and alters T-cell function, modulates cytokine production and cellular migration [53, 54]. Anti-idiotypic antibodies of intravenous immunoglobulin bind to the pathogenic autoantibodies, helping in their rapid decline. Despite partial knowledge of the intravenous immunoglobulin activity, the objective mechanism is not fully understood as it possesses multiple modes of action related to its ability to interact with both innate and adaptive compartment of the immune system [55]. The intravenous immunoglobulin appears to have increased clearance of pathogenic IgG autoantibodies, but failed in the suppression of autoantibody production. However, intravenous immunoglobulin is an adjuvant treatment and suppression of autoantibody production is operated by corticosteroids and other immunosuppressive adjuvants.

The good efficacy and safety profile of intravenous immunoglobulin was documented in multiple reports, mostly small series. The first multicentric, randomized, placebo-controlled, double-blind trial of intravenous immunoglobulin confirmed objectively the efficacy of intravenous immunoglobulin in 61 patients with pemphigus and confirmed a decrease in the autoantibody level in treated patients. After 7 days, anti-Dsg antibody clearance was documented in 42–74.4% of patients [56]. One review study evaluated 23 clinical studies and comprehended data of 260 patients with autoimmune bullous disease treated with intravenous immunoglobulin, among them 191 patients with pemphigus. The intravenous immunoglobulin showed improvement in 245 patients and demonstrated a corticosteroid-sparing effect [57]. In addition, many studies confirmed intravenous immunoglobulin therapy to have a very good safety profile [58, 59].

Some authors offer intravenous immunoglobulin not only for severe and refractory pemphigus vulgaris but also for mild and recalcitrant cases of pemphigus foliaceus [60]. Intravenous immunoglobulin may trigger the shift from an intractable condition to remission using a yet not fully understood mechanism, possibly based on immunomodulation. In recalcitrant pemphigus, a combination of intravenous immunoglobulin and rituximab is recommended. This combination could be useful, when response fails to a high corticosteroid dose in combination with adjuvant immunosuppressive drugs. The mechanism of combined activity of both medications is not known and should be elucidated. However, rituximab affects pathogenic B-cells and blocks production of pathogenic autoantibody and intravenous immunoglobulin rapidly declines pathogenic autoantibody and influences the innate and adaptive immune system. A 10-year follow-up study reported long-lasting remission, in 10 patients with refractory pemphigus vulgaris who have been treated with rituximab combined with intravenous immunoglobulin [9]. The intravenous immunoglobulin preparations are safe and effective and can treat juvenile autoimmune bullous diseases including pemphigus [61]. Several studies reported good safe and efficacy profiles also in pregnancy [38, 62].

An intravenous immunoglobulin response is rapid and administration should be repeated after 4 weeks initially. If the clinical response is good, the interval between cycles could be increased gradually to 6 weeks. If the patient does not respond to an intravenous immunoglobulin therapy, it should be discontinued. In pemphigus vulgaris, the recommended dose is 2 g/kg divided over 3–5 consecutive days. The number of intravenous immunoglobulin cycles should be repeated depending on the severity of disease. In standard regimen, 3–5 cycles are recommended to achieve the desired response. However, severity of the disease may require further intravenous immunoglobulin cycles, without restriction. A repeated dose can be applied also in relapse of the disease. The intravenous immunoglobulin is a relatively safe and well-tolerated therapy. Premedication with an antipyretic, e.g., acetaminophen or antihistamine is recommended to avoid adverse events. Oral or intravenous corticosteroid may be useful, if patient has had a prior reaction or is of elevated risk. The intravenous immunoglobulin should be administered as a long-lasting infusion over 4–5 h.

Systemic adverse events are relatively common, occurring in 20–40% of patients [63], but are mild and most frequently treatable. Immediate adverse reactions account for 60% of all adverse events. They occur during or within 6 h of the infusion and could be avoided by long-lasting infusion. Discontinuation of drug administration may treat immediate adverse events or the treatment is symptomatic. The most frequent immediate adverse event is headache (8.9–43.8%) [63]. Others include muscles aches, fatigue, chills, and fever. Delayed adverse reactions develop within more than 6 h to 1 week after administration. Very rare events occur weeks and months after infusion [63]. A serious adverse event is acute renal failure developing in patients with renal insufficiency. Risk patients are diabetics, older individuals, or patients using concomitantly nephrotoxic agents. Sucrose-free intravenous immunoglobulin preparations are recommended to prevent acute renal failure in risk patients. In these risk patients, an intravenous immunoglobulin should be administered very slowly and at the lowest effective dose. Another serious adverse event is thromboembolism associated with a large dose administered during a fast infusion, which may cause high plasma viscosity. A low dose of intravenous immunoglobulin is imperative also to respect precaution to avoid plasma viscosity.

Thromboembolism may develop within hours, days, or weeks. Risk patients should be monitored. A very rare and serious adverse event is aseptic meningitis, which may develop within 6 h to 1 week [64]. A minimal amount of IgA intravenous immunoglobulin may evoke the production of anti-IgA antibody in patients with IgA deficiency. Subsequently, anti-IgA antibody can cause immediate anaphylactic or anaphylactoid reactions. An intravenous immunoglobulin administration may lead to mild hemolytic reactions, due to the presence of anti-A or anti-B isoagglutinins. Furthermore, mild neutropenia and hyponatremia may occur 2–4 days after infusion and resolves in less than 1 week [63].

Intravenous immunoglobulin is a second-line adjuvant agent and is utilized with corticosteroids or other immunosuppressive adjuvant in refractory pemphigus vulgaris and pemphigus foliaceus. Indication criteria for intravenous immunoglobulin use include the failure of conventional therapy, including significant adverse events in conventional therapy, contraindications to high doses of other immunosuppressive therapies and progressive and rapid uncontrolled disease. However, in exceptional cases intravenous immunoglobulin can be utilized as a first-line treatment, e.g., aseptic bone necrosis, poorly controlled diabetes, advanced osteoporosis, and cataracts. Intravenous immunoglobulin is regarded as a third-line therapy in pemphigus diseases.

3.4.8. Immunoadsorption

Immunoadsorption is a specific method used to selectively clear pathogenic autoantibodies from the circulation in autoantibody-mediated disease, including autoimmune bullous diseases. Immunoadsorption is most frequently used to treat severe and refractory pemphigus vulgaris. In addition, immunoadsorption also removes immune complexes and produces cytapheresis by removing inflammatory cells or platelets from the peripheral circulation. In dermatology, the last can be used to treat pyoderma gangrenosum and psoriasis [65, 66]. Rapid removal of autoantibodies is performed extracorporally by adsorber system, which contains a high-affinity IgG adsorber or low-affinity IgG adsorber. Both adsorber systems differ with respect to ligands, matrix, volume of columns, affinity to certain immunoglobulin classes, and reusability. Reusable adsorbers can be utilized several times for the same patient. The reusable adsorbers are: Immunosorba® (ligand: ligand Staphylococcal protein A), Ig-Therasorb® (ligand: polyclonal anti-human antibodies from sheep), and Globaffin® (ligand: synthetic peptide-PGAM146). Reusable adsorbers are very effective and produce approximately similar depletion rates [67]. A number of one-time adsorbers are available, including adsorber Selesorb® (ligand: dextransulfate), Prosorba® (ligand: Staphylococcal protein A ligand), adsorber IM TR350® (ligand: tryptophan) and IM PH350® (ligand: phenylalanine), and adsorber Coraffin® (ligand: combination of synthetic peptides). One-time use adsorbers achieve only a low degree of IgG decline and usually show little specificity. In the induction phase of therapy, a high-affinity adsorber is recommended. Autoantibody levels can drop by about 75% utilizing a single procedure with a reusable adsorber system. A decrease about of 95% can be reached at the end of one cycle; 3 procedures applied over 3 consecutive days. The 3-day procedure is necessary to avoid a rebound phenomenon, which can appear after the first procedure within 24 h. Autoantibodies re-diffuse from the tissue to circulation and may reach 40% of the initial autoantibody level [68]. In selected cases, the induction phase could be realized with two consecutive treatments with

low-affinity adsorbers (e.g., IM TR350® and IM PH350®). This procedure is utilized in individuals with known hypersensitivity towards material used in columns or other materials. After reaching control of disease, the therapy protocol may continue with subsequent regimen depending on clinical outcome. Single immunoadsorption can be utilized in weekly intervals and later in longer intervals. Another modality is to use a 3- to-4-day procedure repeated monthly. In pemphigus patients, the level of anti-Dsg IgG autoantibody should be evaluated regularly before and after each individual procedure using ELISA or the titer in indirect immunofluorescence. For pemphigus, a new adsorber system is developing with new highly specific adsorber selectively binding anti-Dsg IgG antibodies. Recombinant full-length Dsg1 and Dsg3 ectodomains could be used as a ligand in a highly specific adsorber system [69].

In general, immunoadsorption is recommended to treat severe autoimmune disease, including pemphigus vulgaris in combination with immunosuppressive medication, which can decrease the production of pathogenic autoantibodies. A retrospective study evaluated data of 82 patients with pemphigus treated with immunoadsorption. In most patients, reusable systems were applied with corticosteroids combined with other immunosuppressive drugs, usually azathioprine, mycophenolate mofetil, or cyclophosphamide used in conventional doses. Immunoadsorption showed a sharp decline of anti-Dsg IgG autoantibodies followed by clinical improvement [70]. The recent combination of immunoadsorption with rituximab and immunosuppressive adjuvants azathioprine or mycophenolate mofetil showed complete remission in 88% of patients with autoimmune bullous diseases, including pemphigus vulgaris (6 patients). The combination regimen evokes long-lasting improvement in disease outcome. However, the relapse rate was 13% with an average follow-up of 22 months [71]. In addition, another recent protocol used immunoadsorption combined with rituximab and dexamethasone pulses in conjugation with azathioprine or mycophenolate mofetil, all medication used in conventional doses. Autoantibody levels declined by more than 50% between the first two cycles. This combined regimen demonstrated a long-lasting complete remission in 83% of patients. However, at follow up of 11–43 months a relapse occurred in 26% of patients. In general, the therapy was well tolerated. However, severe adverse events were documented in 9% of patients, including Staphylococcal sepsis and transient paraplegia of the legs [72]. Immunoadsorption combined with another immunosuppressive medication showed a corticosteroid-sparing effect.

Adverse events in immunoadsorption are rare and may occur in ≤1% of procedures [68]. Some severe adverse effects were referred, including deep venous thrombosis, perforating diverticulitis, and sepsis [72]. Other adverse effects may develop such as hypotension, bradycardia, citrate-induced paresthesia, and hypocalcemia [67]. Contraindications for immunoadsorption include known hypersensitivity towards material used in the columns, treatment with ACE inhibitors and anticoagulants, severe cardiovascular disease, hypofibrinogenemia, severe systemic infection and body weight under 15 kg.

Immunoadsorption is a second-line adjuvant treatment in autoimmune bullous disease, including pemphigus. Immunoadsorption is indicated in acute severe disease, if the first-line treatment proved ineffective or is contraindicated. It is a rapid acting mode of treatment and is recommended if a rapid response is required. It can also be used in chronic refractory disease, if the response to standard treatment is inadequate. Immunoadsorption is almost always

utilized in combination with immunosuppressive agents that reduce the production of pathogenic autoantibodies. Systemic corticosteroids are used in high dose orally or intravenously in bolus and usually are combined with adjuvant immunosuppressant, e.g., azathioprine, mycophenolate mofetil or cyclophosphamide. Immunoadsorption is regarded as a third-line therapy in pemphigus diseases.

3.5. Therapy of pemphigus herpetiformis

Pemphigus herpetiformis is a very rare variant in the pemphigus group. The clinical symptoms resemble dermatitis herpetiformis, but the pathogenic autoantibody IgG is directed mostly against Dsg1 (occasionally against Dsg3 or desmocollin) [73]. In general, the prognosis is more favorable than in pemphigus vulgaris. Furthermore, some cases may progress into pemphigus vulgaris, requiring more aggressive treatment. The therapy regimen of pemphigus herpetiformis differs from that of pemphigus vulgaris. Dapsone 100–300 mg/day is utilized as a treatment of choice and can be combined with low dose of systemic corticosteroids. In some severe disease, improvement of disease could be induced with adjuvant agents that are used to treat pemphigus vulgaris. Several authors referred to the good efficacy and tolerability of adjuvant agents, including azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamides [74, 75]. In refractory disease, intravenous immunoglobulin and plasmapheresis may improve the clinical outcome [73]. One case series report of 8 patients with pemphigus herpetiformis referred to the minimal clinical improvement of two patients treated with rituximab [74].

3.5.1. Therapy of IgA pemphigus

IgA pemphigus is a very rare variant of the pemphigus group. Disease differs in clinical affliction from those in the pemphigus group, because of the pustular lesions accompanied by vesicular ones. Based on clinical and pathological symptoms, it is divided into two variants: the subcorneal pustular dermatosis type and intraepidermal neutrophilic IgA dermatosis type. Pathogenic autoantibodies IgA are most frequently directed against desmocollin-1 and desmocollin-2, -3. Occasionally, IgA autoantibodies can be directed against Dsg1 and Dsg3 [76]. Dapsone is regarded as a first-line treatment. A dose of 100–300 mg/day may improve clinical symptoms of IgA pemphigus. Dapsone can be combined with a low dose of corticosteroids. Refractory cases could utilize etretinate or acitretin (50 mg/day), which can be used alone or in combination with dapsone [77, 78]. No objective clinical study was performed to demonstrate the efficacy and tolerability of various therapy regimens in IgA pemphigus. All recommendations result from clinical experience and small series or case reports.

3.5.2. Therapy of paraneoplastic pemphigus (paraneoplastic autoimmune syndrome)

Paraneoplastic pemphigus or paraneoplastic autoimmune syndrome is a rare condition with a variety of lesions including florid oral involvement, generalized polymorphous cutaneous rash resembling various skin disorders and pulmonary involvement. Moreover, it is associated with malignant neoplasm, most frequently hematoblastosis like non-Hodgkin's lymphoma, chronic lymphocytic leukemia or thymoma. However, paraneoplastic pemphigus may occasionally accompany benign neoplasia like Castleman's disease

or monoclonal gammopathy. Therapy of paraneoplastic pemphigus is almost always very difficult and suboptimal. The mainstay of therapy is to treat underlying neoplasm. Early detection and complete resection of neoplasm are of paramount importance. Subsequently, the removal of neoplasm reduces the production of autoantibodies released from the tumor. Perioperative intravenous immunoglobulins administration in an obvious dose (2 g/kg/cycle) is recommended to block autoantibody release from the tumor during surgery [79]. In the case of benign neoplasm, surgical removal ameliorates the condition and may induce remission of paraneoplastic pemphigus with contemporary decrease of autoantibodies within 6–8 weeks [80]. In malignant neoplasm, the prognosis is poor and depends on the behavior of malignant tumor and development of severe respiratory failure. The mortality rate is high and ranges from 75 to 90% [80]. The disease may progress despite surgery and chemotherapy. The prognosis of paraneoplastic pemphigus is obviously unfavorable with rapid fatal outcome. Treatment of clinical symptoms of paraneoplastic pemphigus can be started with systemic corticosteroid, prednisone 0.5–1.0 mg/kg. Adjuvant agents with corticosteroid-sparing effect including azathioprine, mycophenolate mofetil, and cyclophosphamide in conventional doses could be used, but they have mostly potentially tumorigenic properties and their utilization in this condition is limited. However, patients are often resistant to all conventional therapies and therefore a new therapy regimen should be sought. The preferred treatment in paraneoplastic pemphigus is rituximab, which could probably reduce the risk of tumorigenicity. Several studies referred to the efficacy of rituximab, and some of them about rituximab combined with intravenous immunoglobulin. In several cases, rituximab was combined with chemotherapy depending on underlying malignancy [81]. Separaliter administration of intravenous immunoglobulin may also ameliorate the clinical outcome of paraneoplastic pemphigus and has a corticosteroid-sparing effect [59]. Reports about treatment efficacy and tolerability in paraneoplastic pemphigus embrace only small series or case reports. In addition, the therapy protocol embraces aggressive immunosuppressive agents and adverse events are the rule, including serious infections; among them sepsis is the most frequent cause of death. Respiratory failure, if evident, is a fatal complication. Other fatal complications may result from underlying neoplasm.

4. Therapy of bullous pemphigoid group

Bullous pemphigoid is the most frequent autoimmune blistering disorder and may last several years in the absence of treatment followed by total remission. The tendency to relapse is obligate and can be evoked with/without any risk factors. In general, the course of bullous pemphigoid is less severe and requires less aggressive treatment than pemphigus vulgaris (**Table 2**). However, a very severe course of bullous pemphigoid is not excluded. Relapse of disease starts with pruritus, consequently followed by skin eruption and occasionally also oral mucosa involvement. Advanced age in patients supports a large list of comorbidities, including cardiovascular, neurological, neoplastic, metabolic and respiratory comorbidities. The concomitant treatment regimen of comorbidities can hardly influence the choice of treatment regimen in patients with bullous pemphigoid.

First-line therapy	Dose initial therapy
Topical corticosteroid	High potency corticosteroid up 30–40 g/day
Prednisolone	0.5–0.75 mg/kg/day
Second-line therapy (first-line adjuvant agent)	
Tetracyclines	Oxytetracycline 2 g/day, doxycycline 200 mg/day
Azathioprine	1–3 mg/kg/day
Mycophenolate mofetil	2 g/day
Mycophenolic acid	1440 mg/day
Dapsone	100 mg/day or up to ≤1.5 mg/kg/day
Methotrexate	10–20 mg/week
Cyclophosphamide	500 m i.v. bolus or 2 mg/kg/day orally
Third-line therapy (second-line adjuvant agent)	
Anti-CD20 monoclonal antibody (rituximab)	2×1 g i.v. (2 weeks apart) or 4×375 mg/m^2 (each 1 week apart)
Intravenous immunoglobulin G	2 g/kg/4 weeks i.v.
Immunoadsorption	2 cycles a 4 days, 4 weeks apart
Linear IgA dermatosis	
Prednisolone	0.25–0.5 mg/kg/day
Dapsone	100 mg/day
Epidermolysis bullosa acquisita	
Prednisolone	1–1.5 mg/kg/day
Dapsone	25–100 mg/day
Colchicine	0.6–1.2 mg/day
Dermatitis herpetiformis	
Gluten-free diet	
Dapsone	50–150 mg/day

In mild bullous pemphigoid, a topical high potency corticosteroid may control disease. Systemic corticosteroids are used in severe disease; compared with pemphigus in lower doses. Tetracycline has an anti-inflammatory efficacy and can replace corticosteroids in mild bullous pemphigoid. Second-line therapy is used in refractory disease with precaution to comorbidities. The third-line adjuvant agents most frequently are used in severe mucous membrane pemphigoid or epidermolysis bullosa acquisita. Antihistamines are used to eliminate pruritus.

Table 2. The treatment of pemphigoid group.

4.1. Topical and systemic corticosteroids

Bullous pemphigoid can occur as localized or limited disease with mild activity. Potent topical corticosteroids, e.g., clobetasol propionate 0.05% cream or ointment is often successful to achieve remission. A dose up to 30–40 g/day can be administered twice daily to the blisters and erosions and perilesional normal skin. Initial treatment should be tapered 15 days after disease control. The tapering regimen embraces the application of corticosteroid cream or ointment every 2 days in the second month, then twice per week in the third month, and then once per week in the fourth month [82]. In relapse, topical corticosteroid

therapy is increased to the previous level. High-potency topical corticosteroids are also recommended to support healing of more severe disease. Application can cover the whole body, sparing the face. However, administration of high potency corticosteroid to a large body area results in systemic absorption. Despite this, topical application of corticosteroids decreases adverse events of systemic corticosteroids. Topical corticosteroids are recommended in mild disease, especially when localized. However, topical corticosteroids can also be utilized in severe disease as they can decrease the dose of systemic corticosteroids. A large comparative study of 312 patients with bullous pemphigoid demonstrated that mild regimen of topical corticosteroid (10–30 g/day) induced co-equal clinical improvement as that of standard regimen (40 g/day). In addition, a mild regimen of topical corticosteroid allowed a 70% reduction in the cumulative doses of topical potent corticosteroid [83]. Application of topical corticosteroids requires nursing care and should be accompanied by antiseptic bath, bullae count, and bandaging.

Systemic corticosteroids are a mainstay of therapy and are used in lower doses than in pemphigus. Severe bullous pemphigoid is treated with prednisolone 0.5–0.75 mg/kg/day as an initial treatment. Prednisolone dose ≤0.5 mg/kg/day seems to be ineffective. Initial therapy starts with prednisolone 0.5 mg/kg/day and can be increased to 0.75 mg/kg/day only if control of disease is not achieved within 1–3 weeks [84]. The major goal in bullous pemphigoid is reducing the patient's cumulative dose of systemic corticosteroid. During the consolidation phase, the dose of corticosteroid is tapered 15 days after disease control. However, earlier tapering is possible, if the outcome of diseases is favorable. In the maintenance phase, the lowest dose of corticosteroid (prednisolone 0.1 mg/kg/day) should be achieved within 4–6 months after initiation of treatment [82, 85]. If the patient is in remission on maintenance dose for 3–6 months, treatment may be stopped. Total treatment from initiation phase through consolidation phase up to maintenance phase, is usually 9–12 months [82]. In the case of relapse, the previous dose of corticosteroid is recommended.

Topical and systemic corticosteroids are the first-line treatment recommended for mild to severe bullous pemphigoid.

4.2. Adjuvant therapy

In bullous pemphigoid, immunosuppressive adjuvant therapy is used with high precautions and respect to comorbidities. Adjuvants are used when systemic corticosteroids are limited or contraindicated, e.g., in diabetes, severe osteoporosis or cardiovascular disease. However, adjuvant agents have a corticosteroid-sparing effect and their use in the elderly is limited because of adverse events, which are more frequent in this population. Associated treatment of comorbidities can interact with adjuvant drugs and facilitated the involvement of adverse events.

4.2.1. Tetracycline

Tetracycline is recommended as a first adjuvant agent with anti-inflammatory activity confirmed by reduction of collagenolytic activity [86]. Several small series documented good efficacy and safety profiles of tetracycline and nicotinamide to treat mild to severe bullous pemphigoid [86, 87]. The therapy regimen is almost always combined with topical high potency corticosteroids. One randomized controlled study compared doxycycline (200 mg/day) and prednisolone

(0.5 mg/kg/day) for initial therapy in 256 patients with bullous pemphigoid. Therapy with doxycycline was evaluated as a useful alternative to prednisolone [88]. The recommended regimen is oxytetracycline 2 g/day and doxycycline 200 mg/day, both orally. Tetracycline can be used alone or in combination with nicotinamide up to 2 g/day orally. Nicotinamide, the amide derivate of vitamin B has been referred to having several types of anti-inflammatory activity, including inhibition of proinflammatory cytokines [87]. The combination of both may result in ameliorating of anti-inflammatory activity of bullous pemphigoid. The presence of circulating autoantibody after clearance of skin lesions is probably based on anti-inflammatory properties and not on decline of autoantibody production against the basement membrane zone. Tetracycline is regarded as a second-line therapy in pemphigoid diseases.

4.2.2. First-line adjuvant agents: azathioprine, mycophenolate mofetil, methotrexate, and dapsone

First-line adjuvant agents can be used in the same dose as in pemphigus vulgaris and include azathioprine, mycophenolate mofetil, methotrexate, and dapsone [22, 89, 90]. However, a daily dose in the lower range is most frequently effective and better tolerated in elderly patients. A retrospective review evaluated 35 case reports and case series and comprehended data of 170 patients with bullous pemphigoid treated with dapsone alone or combined with corticosteroids. Clinical remission was achieved in 81% of patients. Adverse events were developed in 37% of patients and in 5% of patients required discontinuation of dapsone. The most frequent adverse event was hemolysis and concomitant anemia, both were dose-dependent and reversible [41]. A small series study compared the efficacy and safety of azathioprine and dapsone in 15 patients with bullous pemphigoid. Both drugs were effective and showed an acceptable safety profile [91]. Another small series study compared the corticosteroid-sparing effect of azathioprine and dapsone in 8 patients with bullous pemphigoid. The corticosteroid-sparing effect was moderately higher in dapsone [92]. A retrospective review evaluated 6 studies comprehending data of 79 patients with bullous pemphigoid treated with methotrexate. Clinical improvement was achieved in 94% of patients [34]. Another small series study evaluated 16 patients with bullous pemphigoid treated with methotrexate combined with prednisone. Eight of 16 patients achieved remission off therapy after 25.3 months and during the 5.5 years of follow-up [93]. A retrospective study evaluated data of 70 patients with bullous pemphigoid treated with low-dose methotrexate (5–15 mg/week) combined with short-term high potent topical corticosteroid (clobetasol propionate). The regimen demonstrated very good efficacy and induced clinical improvement in all patients in a mean time interval of 21.9 days. Long-term disease control was achieved in 76% of patients [94]. Cyclophosphamide is a very effective immunosuppressant, but also toxic agent, and so its use in bullous pemphigoid is limited and not generally recommended.

4.2.3. Second-line adjuvant agents: intravenous immunoglobulin G, rituximab, immunoadsorption

Second-line adjuvant agents are used in severe or refractory bullous pemphigoid nonresponsive to corticosteroids or adjuvants of the first line. They must be used with extreme precaution in respect of adverse events. Second-line adjuvant medications are the same as in pemphigus and are utilized by standard rule. However, the number of patients treated with this modality is much lower compared with pemphigus. The efficacy and safety of second-line adjuvants were

referred to in several small series and case reports [89, 90]. One review study evaluated 7 clinical studies and comprehended data of 69 patients with bullous pemphigoid treated with intravenous immunoglobulin. All of the patients showed clinical remission within 14–27 months of post-intravenous immunoglobulin follow-up. In 10 patients, the titer of both anti-BP180 IgG and anti-BP230 IgG autoantibodies showed a gradual decline and non-detectable titer after 11 months and 10 months, respectively. No serious adverse event was documented in all patients treated with intravenous immunoglobulin [57]. Another review study summarized 16 patients with bullous pemphigoid treated with rituximab; among them 14 patients were treated according to the lymphoma protocol and 2 patients according to the rheumatoid arthritis protocol. Complete clinical remission was achieved in 69% of patients and 6% of patients did not show any response. The mortality rate was 19%. Two patients died from sepsis and one from cardiac event [95]. The combination of intravenous immunoglobulin and rituximab showed good efficacy and no serious adverse events in 12 patients with severe and refractory bullous pemphigoid, who did not respond to previous conventional immunosuppressive therapy. Complete clinical improvement was achieved in a mean of 4.6 months and previous immunosuppressive therapy was discontinued. Clinical improvement was correlated with rapid decline of anti-BP180 IgG and anti-BP230 IgG autoantibodies and thereafter remained undetected. The therapy regimen was well tolerated without adverse events, including infections. Ten patients remained in remission in the follow-up at 73.8 months [96]. This regimen could be recommended, if conventional therapy fails. Patients with bullous pemphigoid and elevated level of IgE and eosinophilia who do not respond to conventional therapy regimen could be treated with omalizumab, monoclonal antibody that binds to and declines IgE. It is expected that the anti-BP180 IgE autoantibody could be pathogenic in some individuals [97].

Immunoadsorption can be used in severe refractory autoimmune bullous diseases has shown utilization in bullous pemphigoid not responsive to conventional treatment. Only small case series, or several patients were included into a group of pemphigus patients treated with immunoadsorption. Respectable patients for this regimen are those with markedly elevated levels of pathogenic autoantibodies. Clinical improvement is associated with rapid decline of anti-BP180 IgG and anti-BP230 IgG autoantibodies [67, 68, 70, 98]. Depending on the disease outcome, immunoadsorption can be used in several cycles. Adverse events do not differ from those in pemphigus patients and the incidence is low. One case series study documented good efficacy and safety of immunoadsorption combined with rituximab in various severe and refractory autoimmune bullous diseases, including bullous pemphigoid (3 patients), mucous membrane pemphigoid (3 patients), and epidermolysis bullosa acquisita (1 patients). Concomitant medication with systemic corticosteroids and other immunosuppressive drugs was administered. The clinical improvement was compounded with persistent decrease in both anti-BP180 IgG and anti-BP230 IgG autoantibodies. Complete remission was achieved in all patients and, in one patient, all immunosuppressive therapy was interrupted. Combined therapy proved rapid with long-lasting response, and was well tolerated and produced a corticosteroid-sparing effect [71]. Immunoadsorption is a second-line adjuvant treatment in autoimmune bullous disease including bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita. These second-line adjuvant agents are regarded as a third-line therapy in pemphigoid diseases.

4.3. Therapy of pemphigoid gestationis

Treatment of pemphigoid gestationis is influenced by pregnancy and should be secure to the fetus. In general, treatment is based on clinical experience. Disorder is almost always self-limiting, but can be associated with post-partum relapse. The goal of the therapy is to reduce pruritus and block the production of autoantibodies. Topical high-potency corticosteroids are the first-line therapy. Usually, topical corticosteroids are combined with systemic antihistamine which is respectable in pregnancy, e.g., chlorpheniramine or cetirizine. If the topical corticosteroid is ineffective, a systemic corticosteroid at a low-mild dose is recommended, e.g., prednisolone up to 0.25 mg/kg/day, as an initial dose with subsequent reduction based on clinical outcome [90, 99]. Severe cases require a high dose of 0.5–1 mg/kg/day of prednisolone [100]. Small and moderate doses of systemic corticosteroid do not affect pregnancy and the fetus, whereas placental enzyme inactivates 88% of prednisolone [101]. The initial dose should continue for 1–2 weeks after disease control is reached, then gradually tapered to an adequate maintenance dose. Alternate day therapy is preferred [102]. Discontinuation of prednisolone therapy depends on the clinical outcome and can be realized after or before delivery. In addition, prednisolone is excreted in breast milk in small amount. A dose up to 40 mg/day is regarded as safe [101]. Severe disease can be treated with intravenous immunoglobulin in a conventional dose. The safety profiles of intravenous immunoglobulin in pregnant women were confirmed by several clinical studies in pregnant women with pemphigus [38, 62]. Another choice of treating severe disease and unresponsive disease to conventional treatment is immunoadsorption [70]. One case report referred to a pregnant patient with severe pemphigoid gestationis who was successfully treated with immunoadsorption followed by systemic corticosteroids. After three procedures, disease control was achieved and pathogenic autoantibodies declined by 89% [103]. Immunoadsorption was evaluated as an effective and safe treatment modality in pemphigoid gestationis.

4.3.1. Therapy of linear IgA dermatosis

IgA dermatosis is a rare diagnosis that can affect adults, especially women of fertile age and children. Treatment should be started with topical high-potency corticosteroids. If topical therapy is ineffective, a systemic corticosteroid should be started, e.g., prednisolone in a dose of 0.25–0.5 mg/kg/day. In severe cases, when corticosteroids do not achieve disease control, prednisolone should be combined with dapsone 1 mg/kg/day. It is recommended to initiate the treatment with dapsone 0.5 mg/kg/day to avoid adverse effects, e.g., hemolytic anemia. According to the clinical outcome, initial therapy can be enhanced up to a conventional dose of 100 mg/day or up to ≤1.5 mg/kg/day. In children, dapsone 0.5–2 mg/kg/day is utilized [89]. Another treatment option is tetracycline (2 g/day) combined with nicotinamide (1.5–2 g/day) [104]. A gluten-free diet is ineffective.

4.3.2. Therapy of mucous membrane pemphigoid (cicatricial pemphigoid)

Treatment of mucous membrane pemphigoid is usually very difficult because of the sequela that may result in blindness and esophageal stricture despite utilization of immunosuppressive medications. The therapy regimen is based on whether ocular mucosa is afflicted or not.

Mucous membrane pemphigoid without ocular involvement requires systemic corticosteroids, e.g., prednisolone over 1 mg/kg/day combined with first-line adjuvant agents like dapsone, azathioprine or mycophenolate mofetil [105]. All immunosuppressive agents are used in conventional doses. The preferred medication in mild disease is dapsone being effective in 30–70% of patients. Response to dapsone can be expected within 2–12 weeks [89]. Mucous membrane pemphigoid with ocular involvement has more severe outcome of disease. In mild-to-moderate ocular mucous membrane pemphigoid, dapsone is recommended at a dose of 50 mg/day up to a maximum dose of 200 mg/day. Another choice, especially if dapsone cannot be used, is to utilize sulfapyridine (500 mg/day or two times daily), or sulfasalazine (1–4 g/day). The anti-inflammatory activity of the last three medications is used in the therapy regimen [106]. A retrospective study of 23 patients with mucous membrane pemphigoid with ocular involvement referred to the good efficacy of mycophenolate mofetil. Control of conjunctival inflammation was achieved in 69.6% of patients within 6 months and in 82.6% of patients within 12 months of therapy [107]. In patients with ocular involvement, another choice is a low dose methotrexate. A retrospective clinical study of 17 patients with mucous membrane pemphigoid demonstrated an improvement in ocular inflammation in 72% of afflicted eyes and improvement of visual acuity in 85% of eyes [108]. Progressive disease in ocular involvement requires a more aggressive therapy regimen. Systemic corticosteroid (prednisolone 1 mg/kg/day) with second-line adjuvant agent, like cyclophosphamide (1–2 mg/kg/d), is recommended. A retrospective study of 94 patients documented the good efficacy of cyclophosphamide combined with prednisolone, resulting in total remission of conjunctival inflammation in 82.9% of patients within 1 year [109]. Recently, new strategies have been employed to treat a severe refractory disease. Small series documented the good efficacy and tolerability of intravenous immunoglobulin. Ten patients with progressive ocular involvement in mucous membrane pemphigoid who were unresponsive to conventional immunosuppressive therapy reported good efficacy and tolerability of intravenous immunoglobulin after receiving 4–12 cycles. Clinical improvement and stabilization of ocular disease was achieved in all patients [110]. Another choice is rituximab. One retrospective study documented the efficacy of rituximab to 61 eyes of 32 patients with ocular involvement in mucous membrane pemphigoid. Twenty-six patients achieved clinical remission with an absence of progressive ocular scarring and ocular inflammation within ≥2 months (average remission of 24.5 months). The therapy regimen of rituximab was used as a monotherapy (6 patients) or in combination (6 patients), rituximab combined with intravenous immunoglobulin (14 patients) and rituximab combined with intravenous immunoglobulin and other immunosuppressive adjuvant (6 patients). The progression of ocular involvement was controlled and no cicatrization developed in the follow-up. Adverse effects were mild and transient [111].

4.3.3. Therapy of epidermolysis bullosa acquisita

It is very difficult to treat epidermolysis bullosa acquisita, especially the classic mechano-bullous form associated with high skin fragility at trauma-prone areas. This form is associated with dystrophic changes, digital contracture and esophageal stricture. Inflammatory epidermolysis bullosa acquisita resembles other autoimmune bullous diseases with responses to anti-inflammatory and immunosuppressive medications. The main stay therapy is systemic

corticosteroids, prednisolone 1–1.5 mg/kg/day. Adjuvant agents with corticosteroid-sparing effect used to treat other autoimmune bullous disease are also effective in the management of epidermolysis bullosa acquisita. Such adjuvants include azathioprine (1–2 mg/kg/day), mycophenolate mofetil (1–2 g/day), methotrexate (7.5 mg/week), and cyclophosphamide (500 mg /day in mode of pulse therapy). In small series, anti-inflammatory drugs including dapsone (25–100 mg/day) and colchicine (0.6–1.2 mg/day) induced remission [112]. Colchicine can be used as a single or combined with systemic corticosteroid or dapsone. Adverse events of colchicine include diarrhea, and renal or hepatic toxicity [113]. One retrospective study of 30 patients with epidermolysis bullosa acquisita referred to the time remission of combined methylprednisolone with mycophenolate mofetil or cyclophosphamide or azathioprine. One year after initiation therapy, complete remission was achieved in 33.3% of patients and partial remission in 32.8% [114]. In severe and refractory cases unresponsive to conventional therapy regimen, intravenous immunoglobulin, rituximab, plasmapheresis, and immunoadsorption could be utilized in conventional doses for autoimmune bullous diseases. All of the therapy modalities were used and documented only in small series of patients with epidermolysis bullosa acquisita, almost always with good efficacy and total or partial remission. In all regimens, a good safety profile was documented. Adverse events did not differ from adverse events in other autoimmune bullous disease [115]. Rituximab combined with intravenous immunoglobulin was referred in 5 patients with refractory epidermolysis bullosa acquisita. Patients received a high number of intravenous immunoglobulin (10–26) and 1–2 cycles of rituximab and achieved adequate improvement of disease, while being well tolerated [116]. The education of patients in the management of topical therapy and preventive measures against common trauma are obligatory.

5. Therapy of dermatitis herpetiformis

The mainstay therapy in dermatitis herpetiformis is a gluten-free diet that ameliorates both skin disease and gluten sensitive enteropathy. Precise maintenance of a gluten-free diet of 2 years cleans the skin disease and heals enteropathy. Adherence to a gluten-free diet should be provided for the whole life. After many years, IgA-antibody deposits disappear from the dermo-epidermal junction in both bowel and skin [6]. The reintroduction of gluten to the diet evokes the recurrence of gluten sensitive enteropathy and cutaneous rash within 12 weeks, frequently sooner. Good adherence to a gluten-free diet within 5–10 years induces improvement of enteropathy and is regarded to have a protective property against lymphoma, which might be associated with dermatitis herpetiformis [117]. Patients on a gluten-free diet must exclude cereals containing gluten and its toxic fractions, including wheat, rye, and barley. Based on some authors, oats can be incorporated into a gluten-free diet, whereas the majority of patients with dermatitis herpetiformis and gluten-sensitive enteropathy can tolerate moderate amounts of pure oats [118, 119]. Furthermore, oats increase the nutrition value of a gluten-free diet. Some studies reported that pure oats do not induce systemic or mucosal antibody response in patients with coeliac disease [119, 120]. However, oats can be contaminated with prolamines from other cereals and pure oats are difficult to prepare. This issue requires further investigation and new agricultural processing and manufacture of oats. Long-term

administration of a gluten-free diet could permit the discontinuation of systemic medication, meaning self-sustaining treatment in dermatitis herpetiformis.

The mainstay medication in dermatitis herpetiformis is dapsone at a dose of 50–150 mg/day. Dapsone usually has a rapid and dramatic effect in suppressing skin symptoms within a few days, but does not have a curable effect on the underlying enteropathy. The effectiveness of dapsone has not been confirmed by clinical studies. Multiple and long-lasting empirical utilization of dapsone in practice confirmed its efficacy and safety in dermatitis herpetiformis.

Another choice to treat dermatitis herpetiformis is sulfonamides, when dapsone fails to control the disease or is not tolerated. Three sulfonamides may be an alternative to dapsone: sulfapyridine (1.5 g/day), sulfamethoxypyridazine (0.25–1.5 g/day), and sulfasalazine (1–2 g/day) [6]. Several case reports referred to an alternative treatment using sulfasalazine, which is commonly utilized in the long-term management of inflammatory bowel disease and as a second-line agent in rheumatoid arthritis and psoriatic arthritis [121]. All three sulfonamides may cause the same adverse events, including hypersensitivity reactions and bone marrow toxicity, resulting in agranulocytosis, aplastic anemia, and methemoglobinemia. More common and not severe adverse effects are nausea, anorexia, and vomiting. Gastro-enteric events could be avoided with administration of an enteric-coated form of medication.

Systemic corticosteroids are not recommended for treating dermatitis herpetiformis, because they are not effective. On the other hand, topical corticosteroids, especially of high potency (e.g., clobetasol propionate) may reduce itching. Another choice to ameliorate pruritus is third-generation antihistamine with specific activity on eosinophil activity.

6. Local therapy in autoimmune bullous diseases

In autoimmune bullous disease, the local therapy is important to prevent infection, to control reepithelization of denuded areas, and to ameliorate pain. Management of bullae depends on their size. Small bullae stay intact and large bullae should be punctured, but the covering should stay at the site of previous bullae. The released roof of blister built up a protective covering that shield the denuded area from secondary infection as well as loss of serum contents. In extensive disease, bathing with antiseptic agent should be applied, e.g., potassium permanganate (1:10,000), chlorhexidine or other commercial agent. Denuded areas should be covered with antiseptic or antibiotic agent in the form of lotions, sprays or cream. A potent topical corticosteroid, e.g., 0.05% clobetasone propionate cream, is preferably used in bullous pemphigoid and can be the self-sustaining therapy in mild bullous pemphigoid [82]. The advantage of topical corticosteroids is their local anti-inflammatory and immunosuppressive activity, which may be helpful in dropping of the systemic corticosteroid. Topical corticosteroids are also successfully utilized to treat minor forms of pemphigus or in the maintenance phase of therapy management [122]. One clinical study demonstrated the good efficacy of clometasone propionate 0.05% cream applied to afflicted areas on skin and mucosa in 7 patients with pemphigus vulgaris and pemphigus foliaceus. Topical corticosteroid was used as self-sustaining therapy. Another topical corticosteroid, betamethasone valerate 0.1% cream,

was applied to the face. The creams were used twice daily for at least 15 days, up to remission. Moreover, when clinical improvement was achieved, topical creams were applied in tapering mode to the area of previous lesions. In 4 patients, relapses occurred when topical treatment was discontinued, but were successfully controlled by reapplication of topical corticosteroid. In 3 patients, topical therapy failed, and a systemic corticosteroid was utilized and combined with other adjuvant agents (dapsone or methotrexate). Topical treatment did not influence anti-Dsg IgG autoantibody titer. No serious side effect was noticed [123]. Topical corticosteroids seem to have only postponed activity in autoimmune bullous disease, because they do not influence the production of pathogenic autoantibody and utilize only anti-inflammatory activity. However, topical corticosteroids may help bypass the period before the systemic immunosuppressive drug should be used to control disease. In addition, minor disease can be controlled by self-sustained topical corticosteroid. Moreover, the monitoring of pathogenic autoantibody may indicate a relative threat of relapse and utilization of systemic medication. In mild disease, a combination of topical corticosteroid with systemic immunosuppressive agent may induce improvement of clinical outcome. In addition, topical corticosteroids may support the systemic agent and advocate healing through their local anti-inflammatory activity. A topical corticosteroid agent can be combined with antibiotic, e.g., gentamycin having dual activity, anti-inflammatory, and antibacterial.

The therapeutic challenge is the pathologic lesions in mucosa, especially in the oral cavity. The response to conventional therapy in oral mucosa occurs in a special environment resulting in delayed healing compared with skin lesions. Topical administration in mucosa should be modified because the saliva dilutes and shortens the therapeutic activity of medication. Therefore, corticosteroid should be implicated into an adhesive paste, which allows longer persistence and activity of the medication. Fluocinonide 0.05%, clobetasol 0.05%, and halobetasol 0.05% ointments compounded 1:1 with Orabase have shown good efficacy in oral management in 12 patients with oral pemphigus vulgaris. The only adverse effect was candida infection in the oral cavity, which afflicted most of the patients [124].

Another option in topical management of the oral cavity is triamcinolone acetonide, a high potency corticosteroid administered perilesional or intralesional to treat recalcitrant and remnant lesions. One clinical study compared perilesional or intralesional triamcinolone acetonide application and topical cream of 0.1% in 35 patients with recalcitrant oropharyngeal pemphigus vulgaris. Perilesional or intralesional triamcinolone displayed a better clinical outcome than topical application and induced complete clinical remission, while reducing the total amount of corticosteroids [125]. A perilesional or intralesional corticosteroid is recommended only in the maintenance phase of therapy, when 4–6 oropharyngeal sites are involved and do not respond to conventional immunosuppressive therapy. In addition, immediate use can be recommended to treat new lesions appearing in the maintenance phase. This regimen is not recommended upon relapse of disease, because the first step is to enhance systemic immunosuppressive medication. Good and meticulous personal oral hygiene and periodic professional oral hygiene sessions are advisable. Topical antiseptic mouthwash solution containing anesthetic agent is useful. However, afflicted mucosa especially that of the oral cavity, shows a refractory clinical outcome and slow response to systemic therapy. Perilesional or intralesional triamcinolone acetonide may improve vegetative tissue formation, especially in intertriginous location in pemphigus vegetans [126].

The topical immunomodulatory agents, calcineurin inhibitors, are new choice in local management of autoimmune bullous disease that promote healing and may enhance reepithelization. A double-blind, placebo-controlled clinical study referred to the good efficacy and safety profile of pimecrolimus 1% cream for cutaneous lesions in 11 patients with pemphigus vulgaris [127]. Another new topical agent, epidermal growth factor (10 μg in cream) was evaluated in a double-blind, randomized, controlled clinical trial and showed accelerating efficacy and a good safety profile in 20 patients with cutaneous lesions of pemphigus vulgaris [128]. Nicotinamide gel 4%, an adjunctive topical gel, was referred as an effective new treatment modality for cutaneous lesions of pemphigus vulgaris in 8 patients in a double-blind, placebo-controlled study [129]. All new topical medications should be confirmed in large clinical studies and eventually in practice.

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References

[1] Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. Archives of Dermatology. 1996;**16**:203-212 PMID: 8629830

[2] Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z, Barzegari M, Akhiani M, Ghodsi Z, Mortazavi H, Naraghi Z. Pemphigus: Analysis of 1209 cases. International Journal of Dermatology. 2005;**44**:470-476. DOI: 10.1111/j.1365-4632.2004.02501.x

[3] Lee JH, Kim SC. Mortality of patients with bullous pemphigoid in Korea. Journal of the American Academy of Dermatology. 2014;**71**:676-683. DOI: 10.1016/j.jaad.2014.05006

[4] Hertl M, Jedlickova H, Karpati S, Martinovic B, Uzun S, Yayli S, Mimouni D, Borradori L, Feliciani C, Ioannides D, Joly P, Kowalewski C, Zambruno G, Zillikens D, Jonkman MF. Pemphigus. S2 Guideline for diagnosis and treatment-guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). Journal of the European Academy of Dermatology and Venereology. 2015;**29**:405-414. DOI: 10.1111/jdv.12772

[5] Bernad P, Reguiai Z, Tancréde-Bohin E, Cordel N, Platin P, Pauwels C, Vaillant L, Grande F, Richard-Lallemand MA, Sassolas B, Roujeau JC, Lok C, Picard-Dahan C, Chosidow O, Vitry F, Joly P. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: A multicenter, prospective, cohort study. Archives of Dermatology. 2009;**145**:537-542. DOI: 10.1001/archdermatol.2009.53

[6] Caproni M, Antiga E, Melani L, Fabbri P. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. Journal of the European Academy of Dermatology and Venereology. 2009;**23**:633-638. DOI: 10.1111/j.1468-3083.2009.03188.x

[7] Eming R, Sticherling M, Hofmann SC, Hunzelmann N, Kern JS, Kramer H, Pfeifer C, Schuster V, Zillikens D, Goebeler M, Hertl M, Nast A, Orzechowski HD, Sárdy M, Schmidt E, Sitaru C, Sporbeck B, Worm M. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. Journal der Deutschen Dermatologischen Gesellschaft. 2015;**13**:833-844. DOI: 10.1111/ddg.12606

[8] Ratnam KV, Phay KL, Tan CK. Pemphigus therapy with oral prednisolone regimens. A 5-years study. International Journal of Dermatology. 1990;**29**:363-367 PMID: 2361795

[9] Bystryn JC, Rudolph JL. Pemphigus. Lancet. 2005;**366**:61-73. DOI: 10.1016/S0140-6736 (05)66829-8

[10] Herbst A, Bystryn JC. Patterns of remission in pemphigus vulgaris. Journal of the American Academy of Dermatology. 2000;**42**:422-427 PMID: 10688711

[11] Almugairen N, Hospital V, Bedane C, Duvert-Lehembre S, Picard D, Tronquony AF, Houivet E, Díncan M, Joly P. Assessment of the rate of long-term complete remission off therapy in patients with pemphigus treated with different regimens including medium- and high-dose corticosteroids. Journal of the American Academy of Dermatology. 2013;**69**:583-588. DOI: 10.1016/j.jaad.2013.05.016

[12] Patel AA, Swerlich RA, McCall CO. Azathioprine in dermatology: The past, the present, and the future. Journal of the American Academy of Dermatology. 2006;**55**:369-389. DOI: 10.1016/j.jaad.2005.07.059

[13] Meyer V, Beissert S. Azathioprine in the treatment of autoimmune blistering disease. Immunology and Allergy Clinics of North America. 2012;**32**:295-307. DOI: 10.1016/j.iac. 2012.04.009

[14] Chams-Davatchi C, Esmaili N, Daneshpazhooh M, Valikhani M, Balighi K, Hallaji Z, Barzegari M, Akhyani M, Ghodsi SZ, Seifari H, Nazemi MJ, Mortazavi H, Mirshams-Shahshahani M. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. Journal of the American Academy of Dermatology. 2007;**57**:622-628. DOI: 10.1016/j.jaad.2007.05.024

[15] Atzmony L, Hodak E, Gdalevich M, Rosenbaum O, Minouni D. Treatment of pemphigus vulgaris and pemphigus foliaceus: A review and meta-analysis. American Journal of Clinical Dermatology. 2014;**15**:503-515. DOI: 10.1007/s40257-014-0101-9

[16] Atzmony L, Hodak E, Leshem YA, Rosenbaum O, Gdalevich M, Anhalt GJ, Mimouni D. The role of adjuvant therapy in pemphigus: A systemic review and meta-analysis. Journal of the American Academy of Dermatology. 2015;**73**:264-271. DOI: 10.1016/j.jaad.2015.04.038

[17] Martin LK, Werth VP, Villaneuva EV, Murrell DF. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. Journal of the American Academy of Dermatology. 2011;**64**:903-908. DOI: 10.1016/j.jaas.2010.04.039

[18] Uchiyama K, Nakamura M, Kubota T, Yamane T, Fujise K, Tajiri H. Thiopurine S-methyltransferase and inosine triphosphate pyrophosphohydralase genes in Japanese patients with inflammatory bowel disease in whom adverse drug reactions were induced by azathioprine/6-mercaptopurine treatment. Journal of Gastroenterology. 2009;**44**:197-203. DOI: 10.1007/s00535-008-2307-1

[19] Schiavo AL, Puca RV, Ruocco V, Ruocco E. Adjuvant drugs in autoimmune bullous diseases, efficacy versus safety: Facts and controversies. Clinics in Dermatology. 2010;**28**:337-343. DOI: 10.1016/j.clindermatol.2009.06.018

[20] Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. Clinics in Dermatology. 2012;**30**:78-83. DOI: 10.1016/j.clindermatol.2011.03.013

[21] Garritsen FM, van den Broek MP, van Zuilen AD, Fidder HH, de Bruin-Weller MS, Spuls PI. Pregnancy and fetal outcomes after paternal exposure to azathioprine, methotrexate or mycophenolic acid: A critically appraised topic. The British Journal of Dermatology. 2017;**176**:866-877. DOI: 10.1111/bjd.15320

[22] Eskin-Schwartz M, David M, Mimouni D. Mycophenolate mofetil for management of immune bullous diseases. Dermatologic Clinics. 2011;**29**:555-559. DOI: 10.1016/j.det.2011.06.012

[23] Beissert S, Werfel T, Frieling U, Böhm M, Sticherling M, Stadler R, Zillikens D, Rzany B, Hunzelmann N, Meuer M, Gollnick H, Ruzicka T, Pillekamp H, Junghans V, Luger TA. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for treatment of pemphigus. Archives of Dermatology. 2006;**142**:1447-1454. DOI: 10.1001/archderm.142.11.1447

[24] Strowd LC, Taylor SL, Jorizzo JL, Namazi MR. Therapeutic ladder for pemphigus vulgaris: Emphasis on achieving complete remission. Journal of the American Academy of Dermatology. 2011;**64**:490-494. DOI: 10.1016/j.jaad.2010.02.052

[25] Doukaki S, Platamone A, Alaimo R, Bongiorno MR. Mycophenolate mofetil and enteric-coated mycophenolate sodium in the treatment of pemphigus vulgaris and pemphigus foliaceus. Journal of Dermatological Treatment. 2015;**26**:67-72. DOI: 10.3109/09546634.2014.880395

[26] Hashimoto T, Kawakami T, Koga H, Ohyama B, Hamada T, Dainichi T, Nakama T, Yasumoto S, Tsuruta D, Ishii N. Therapeutic effects of mizoribine on pemphigus vulgaris and pemphigus foliaceus. Dermatologic Therapy. 2012;**25**:382-385. DOI: 10.1111/dth.12386

[27] Ahlmann M, Hempel G. The effect of cyclophosphamide on the immune system: Implications for clinical cancer therapy. Cancer Chemotherapy and Pharmacology. 2016;**78**:661-671. DOI: 10.1007/s00280-016-3152-1

[28] Cummins DL, Mimouni D, Anhalt GJ, Nousari CH. Oral cyclophosphamide for treatment of pemphigus vulgaris and foliaceus. Journal of the American Academy of Dermatology. 2003;**49**:276-280. DOI: 10.1067/S0190-9622(03)00859-4

[29] Olszewska M, Kolacinska-Strasz Z, Sulei J, Labecka H, Cwikla J, Natorska U, Blaszczyk M. Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. American Journal of Clinical Dermatology. 2007;**8**:85-92 PMID: 17428113

[30] Sardana K, Agarwal P, Bansal S, Uppal B, Garg VK. A comparative effectiveness research of azathioprine and cyclophosphamide on the clinical and serological response in pemphigus vulgaris. Indian Journal of Dermatology. 2016;**61**:418-426. DOI: 10.4103/0019-5154.185710

[31] Rose E, Wever S, Zilliken D, Linse R, Haustein UF, Bröcker EB. Intravenous dexamethasone-cyclophosphamide pulse therapy in comparison with oral methylprednisolone-azathioprine therapy in patients with pemphigus: Results of a multicentric prospectively randomized study. Journal der Deutschen Dermatologischen Gesellschaft. 2005;**3**:200-206 PMID: 16372814

[32] Chan ES, Cronstein BN. Methotrexate-how does it really work? Nature Reviews Rheumatology. 2010;**6**:175-178. DOI: 1630.1038/nrrheum.2010.5

[33] Shen S, O'Brien T, Yap LM, Prince HM, McCormack CJ. The use of methotrexate in dermatology: A review. The Australasian Journal of Dermatology. 2012;**53**:1-18. DOI: 10.1111/j.1440-0960.2011.00839.x

[34] Gürcan HM, Ahmed R. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. The British Journal of Dermatology. 2009;**161**:723-731. DOI: 10.1111/j.1365-2133.2009.09246.x

[35] Bangert CA, Costner MI. Methotrexate in dermatology. Dermatologic Therapy. 2007; **20**:216-228. DOI: 10.1111/j.1529-8019.2007.00135.x

[36] Chalmers RJ, Kirby B, Smith A, Burrows P, Little R, Horan M, Hextall JM, Smith CH, Klaber M, Rogers S. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: A multicenter audit and health economic analysis. The British Journal of Dermatology. 2005;**152**:444-450. DOI: 10.1111/j.1365-2133.2005.06422.x

[37] Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. Journal of the American Academy of Dermatology. 2009;**60**:824-837. DOI: 10.1016/j.jaad.2008.11.906

[38] Tavakolpour S, Mirasafaei HS, Delshad S. Management of pemphigus disease in pregnancy. American Journal of Reproductive Immunology. 2017;**77**:e1261. DOI: 10.1111/aji.12601

[39] Piette EW, Werth VP. Dapsone in the management of the autoimmune bullous diseases. Dermatologic Clinics. 2011;**29**:561-564. DOI: 10.1016/j.det.2011.06.018

[40] Werth VP, Fivenson D, Pandya AG, Chen D, Rico MJ, Albrecht J, Jacobus D. Multicenter randomized, double-blind, placebo-controlled, clinical trial of dapsone as a glucocorticoid-sparing agent in maintenance-phase pemphigus vulgaris. Archives of Dermatology. 2008; **144**:25-32. DOI: 10.1001/archDerm.144.1.25

[41] Gürcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: Analysis of current data. American Journal of Clinical Dermatology. 2009;**10**:383-396. DOI: 10.2165/11310740-000000000-00000

[42] El-Zawahry B, Bassiouny D, Hegazy R, Gawdat H, Shalaby S, Khoshied M, Saleh MA. Rituximab treatment in pemphigus vulgaris: Effect on circulating T regs. Archives of Dermatological Research. 2017;Jun 19. DOI: 10.1007/s00403-017-1754-z

[43] Borradori L, Lombardi T, Samson J, Girardet C, Saurat JH, Hügli A. Anti-CD20 monoclonal antibody rituximab for refractory erosive stomatitis secondary to $CD20^+$ follicular lymphoma-associated paraneoplastic pemphigus. Archives of Dermatology. 2001;**137**:269-272 PMID: 11255323

[44] Zakka LR, Shetty SS, Ahmed R. Rituximab in the treatment of pemphigus vulgaris. Dermatologic Therapy. 2012;**2**:17. DOI: 10.1007/s13555-012-0017-3

[45] Leshem YA, Hodak E, David M, Anhalt GJ, Mimouni D. Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: A retrospective study of 47 patients. Journal of the American Academy of Dermatology. 2013;**68**:404-411. DOI: 10.1016/j.jaad.2012.08.010

[46] Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, Caillot F, Golinski ML, Labeille B. Picard-Dahan C et French study group on autoimmune bullous diseases. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): A prospective, multicenter, parallel-group, open-label randomized trial. Lancet. 2017;**389**:2031-2040. DOI: 10.1016/S0140-6736(17)30070-3

[47] Cho YT, Lee FY, Chu CY, Wang LF. First-line combination therapy with rituximab and corticosteroids is effective and safe for pemphigus. Acta Dermato-Venereologica. 2014;**94**:472-473. DOI: 10.2340/00015555-1746

[48] Ingen-Housz-Oro S, Valeyrie-Allanore L, Cosnes A, Ortonne N, Hüe S, Paul M, Wolkenstein P, Chosidow O. First-line treatment of pemphigus vulgaris with a combination of rituximab and high-potency topical corticosteroids. JAMA Dermatology. 2015;**151**:200-203. DOI: 10.1001/jamadermatol.2014.2421

[49] Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, Amagai M: Pemphigus. Nature Reviews Disease Primers. 2017;**3**:17026. DOI:10.1038/nrdp.2017.26

[50] Ahmed AR, Nguyen T, Kaveri S, Spigelman ZS. First line treatment of pemphigus vulgaris with a novel protocol in patients with contraindications to systemic corticosteroids and immunosuppressive agents: Preliminary retrospective study with a seven year follow-up. International Immunopharmacology. 2016;**34**:25-31. DOI: 10.1016/j.intimp.2016.02.013

[51] Huang A, Madan RK, Levitt J. Future therapies for pemphigus vulgaris: Rituximab and beyond. Journal of the American Academy of Dermatology. 2016;**74**:746-753. DOI: 10.1016/j.jaad.2015.11.008

[52] Enk A. European Dermatology Forum Giudeline Subcomittee. Guidelines on the use of high-dose intravenous immunoglobulin in dermatology. European Journal of Dermatology. 2009;**19**:90-98. DOI: 10.1684/ejd.2008.0580

[53] Nagelkerke SO, Kuijpers TW. Immunomodulation by IVIG and the role of Fc-gamma receptors: Classic mechanisms of action after all? Frontiers in Immunology. 2015;**5**:674. DOI: 10.3389/fimmu.2014.00674

[54] Czernik A, Toosi S, Bystryn JC, Grando S. Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: An update. Autoimmunity. 2012;**45**:111-118. DOI: 10.3109/08916934.2011.606452

[55] Tha-In T, Bayry J, Metselaar HJ, Kaveri SV, Kwekkeboom J. Modulation of the cellular immune system by intravenous immunoglobulin. Trends in Immunology. 2008;**29**:608-615. DOI: 10.1016/j.it.2008.08.004

[56] Amagai M, Ikeda S, Shimizu H, Iizuka H, Hanada K, Aiba S, Kaneko F, Izaki K, Tamaki K, Ikezawa Z, Takigawa M, Seishima M, Tanaka T, Miyachi Y, Katayama I, Horiguchi Y, Miyagawa S, Furukawa F, Iwatsuki K, Hide M, Tokura Y, Furue M, Hashimoto T, Ihn H, Fujiwara S, Nishikawa T, Ogawa H, Kitajima Y, Hashimoto KA. Randomized double-blind trial of intravenous immunoglobulin for pemphigus. Journal of the American Academy of Dermatology. 2009;**60**:595-603. DOI: 10.1016/j.jaad.2008.09.052

[57] Gürcan HM, Jeph S, Ahmed AR. Intravenous immunoglobulin therapy in autoimmune mucocutaneous blistering diseases: A review of the evidence for its efficacy and safety. American Journal of Clinical Dermatology. 2010;**11**:315-326. DOI: 10.2165/11533290-000000000-00000

[58] Svecova D. IVIG therapy in pemphigus vulgaris has corticosteroid-sparing and immunomodulatory effects. The Australasian Journal of Dermatology. 2016;**57**:141-144. DOI: 10.1111/ajd.12422

[59] Seidling V, Hoffmann JH, Enk AH, Hadaschik EN. Analysis of high-dose intravenous immunoglobulin therapy in 16 patients with refractory autoimmune blistering skin disease: High efficacy and no serious adverse events. Acta Dermato-Venereologica. 2013;**93**:346-349. DOI: 10.2340/00015555-1471

[60] Kawakami T, Koga H, Saruta H, Ueda A, Inoue Y, Soma Z, Ishii N, Hashimoto T. Four mild but refractory cases of pemphigus foliaceus successfully treated with intravenous immunoglobulin. The Journal of Dermatology. 2013;**40**:869-873. DOI: 10.1111/1346-8138.12280

[61] Gürcan HM, Mabrouk D, Ahmed AR. Management of pemphigus in pediatric patients. Minerva Pediatrica. 2011;**63**:279-291 PMID: 21909064

[62] Ahmed AR, Gürcan HM. Use of intravenous immunoglobulin therapy during pregnancy in patients with pemphigus vulgaris. Journal of the European Academy of Dermatology and Venereology. 2011;**25**:1073-1079. DOI: 10.1111/j.1468-3083.2010.03925.x

[63] Stiehm ER. Adverse effects of human immunoglobulin therapy. Transfusion Medicine Reviews. 2013;**27**:171-178. DOI: 10.1016/j.tmrv.2013.05.004

[64] Bharath V, Eckert K, Kang M, Chin-Yee IH, Hsia CC. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis: A retrospective review at a single tertiary care center. Transfusion. 2015;**55**:2597-2605. DOI: 10.1111/trf.13200

[65] Watanabe Y, Yamada H. Leukocyte adsorption apheresis for the treatment of pyoderma gangrenosum. The Journal of Dermatology. 2008;**35**:792-794. DOI: 10.1111/j.1346-8138.2008.00572.x

[66] Liumbruno GM, Centoni PE, Molfettini P, Ceretelli S, Ceccarini M, Bachini L, Pomponi A, Bagnoni G, Vitolo M, Eberle O, Biondi A, Sodini ML. Lymphocytapheresis in the treatment of psoriasis vulgaris. Journal of Clincal Aheresis. 2006;**21**:158-164. DOI: 10.1002/jca.20079

[67] Zillinkens D, Derfler K, Eming R, Fierlbeck G, Goebeler M, Hertl M, Hofmann SC, Karlhofer F, Kautz O, Nitschke M, Opitz A, Quist S, Rose C, Schanz S, Smidt E, Shimanovich I, Sticherling M. Recommendations for the use of immunoapheresis in the treatment of autoimmune bullous diseases. Journal der Deutschen Dermatologischen Gesellschaft. 2007;**5**:881-887. DOI: 10.1111/j.1610-0387.2007.06342.x

[68] Schmidt E, Zillikens D. Immunoadsorption in dermatology. Archives of Dermatological Research. 2010;**302**:241-253. DOI: 10.1007/s00403-009-1024-9

[69] Langenhan J, Dworschak J, Saschenbrecker S, Komorowski L, Schlumberger W, Stöcker W, Westermann J, Recke A, Zillikens D, Schmidt E, Probst C. Specific immunoadsorption of pathogenic autoantibodies in pemphigus requires the entire ectodomains of desmogleins. Experimental Dermatology. 2014;**23**:253-259. DOI: 10.1111/exd.12355

[70] Meyersburg D, Schmidt E, Kasperkiewicz M, Zillikens D. Immunoadsorption in dermatology. Therapeutic Apheresis and Dialysis. 2012;**16**:311-320. DOI: 10.1111/j.1744-9987.2012.01075.x

[71] Kolesnik M, Becker E, Reinhold D, Ambach A, Heim MU, Gollnick H, Bonnekoh B. Treatment of severe autoimmune blistering skin diseases with combination of protein a immunoadsorption and rituximab: A protocol without initial dose or pulse steroid medication. Journal of the European Academy of Dermatology and Venereology. 2014;**28**:771-780. DOI: 10.1111/jdv.12175

[72] Kasperkiewicz M, Shimanovich I, Meier M, Schumacher N, Westermann L, Kramer J, Zillikens D, Schmidt E. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: A pilot study of 23 patients. The British Journal of Dermatology. 2012;**166**:154-160. DOI: 10.1111/j.1365-2133.2011.10585.x

[73] Kasperkiewicz M, Kowalewski C, Jablonska S. Pemphigus herpetiformis: From first description until now. Journal of the American Academy of Dermatology. 2014;**70**:780-787. DOI: 10.1016/j.jaad.2013.11.043

[74] Laws PM, Heelan K, Al-Mohammedi F, Walsh S, Shear NH. Pemphigus herpetiformis: A case series and review of the literature. International Journal of Dermatology. 2015;**54**:1014-1022. DOI: 10.1111/ijd.12582

[75] Duarte IB, Bastazini I, Barreto JA, Carvalho CV, Nunes AJ. Pemphigus herpetiformis in childhood. Pediatric Dermatology. 2010;**27**:488-491. DOI: 10.1111/j.1525-1470.2010.01256.x

[76] Hashimoto T, Teye K, Ishi N. Clinical and immunological studies of 49 cases of various types of intercellular IgA dermatosis and 13 cases of classical subcorneal pustular dermatosis examined at Kurume University. The British Journal of Dermatology. 2017;**176**:168-175. DOI: 10.1111/bjd.14780

[77] Tsuruta D, Ishii N, Hamada T, Ohyama B, Fukuda S, Koga H, Imamura K, Kobayashi H, Karashima T, Nakama T, Dainichi T, Hashimoto T. IgA pemphigus. Clinics in Dermatology. 2011;**29**:437-442. DOI: 10.1016/j.clindermatol.2011.01.014

[78] Monshi B, Richter L, Hashimoto T, Groiß E, Haensch N, Rappersberger K. IgA pemphigus of the subcorneal pustular dermatosis type. Successful therapy with a combination of dapsone and acitretin. Der Hautarzt. 2012;**63**:482-486. DOI: 10.1007/s00105-011-2270-2

[79] Yong AA, Tey HL. Paraneoplastic pemphigus. The Australasian Journal of Dermatology. 2013;**54**:241-250. DOI: 10.1111/j.1440-0960.2012.00921.x

[80] Wieczorek M, Czernik A. Paraneoplastic pemphigus: A short review. Clinical, Cosmetic and Investigational Dermatology. 2016;**9**:291-295. DOI: 10.2147/CCID.S100802

[81] Czernik A, Camilleri M, Pittelkow MR, Grando SA. Paraneoplastic autoimmune multiorgan syndrome: 20 years after. International Journal of Dermatology. 2011;**50**:905-914. DOI: 10.1111/j.1365-4632.2011.04868.x

[82] Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, Kowalewski C, Jedlickova H, Kárpáti S, Marinovic B, Mimouni D, Uzun S, Yayli S, Hertl M, Borradori L. Management of bullous pemphigoid: The European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. The British Journal of Dermatology. 2015;**172**:867-877. DOI: 10.1111/bjd.13717

[83] Joly P, Roujeau JC, Benichou J, Delaporte E, D'Incan M, Dreno B, Bedane C, Sparsa A, Gorin I, Picard C, Tancrede-Bohin E, Sassolas B, Lok C, Guillaume JC, Doutre MS, Richard MA, Caux F, Prost C, Plantin P, Chosidow O, Pauwels C, Maillard H, Saiag P, Descamps V, Chevrant-Breton J, Dereure O, Hellot MF, Esteve E, Bernard P. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: A multicenter randomized study. The Journal of Investigative Dermatology. 2009;**129**:1681-1687. DOI: 10.1038/jid.2008.412

[84] Culton DA, Diaz LA. Treatment of subepidermal immunobullous diseases. Clinics in Dermatology. 2012;**30**:95-102. DOI: 10.1016/jclindermatol.2011.03.015

[85] Bagci IS, Horváth ON, Ruzicka T, Sárdy M. Bullous pemphigoid. Autoimmunity Reviews. 2017;**16**:445-455. DOI: 10.1016/j.autrev.2017.03.010

[86] Henehan M, Montuno M, De Benedetto A. Doxycycline as an anti-inflammatory agent: Updates in dermatology. Journal of the European Academy of Dermatology and Venereology. 2017;**31**:1800-1808. DOI: 10.1111/jdv.14345

[87] Siohara J, Yoshida K, Hasegawa J, Uhara H, Takata M, Saida T, Ohyama B, Hashimoto T. Tetracycline and niacinamide control bullous pemphigoid but not pemphigus foliaceus when these conditions coexist. The Journal of Dermatology. 2010;**37**:657-661. DOI: 10.1111/j.1346-8138.2010.00920.x

[88] Chalmers JR, Wojnarowska F, Kirtschig G, Nunn AJ, Bratton DJ, Mason J, Foster KA, Whitham D, Williams HC. A randomized controlled trial to compare the safety and effectiveness of doxycycline (200 mg daily) with oral prednisolone (0.5 mg kg^{-1} daily) for initial treatment of bullous pemphigoid: A protocol for the bullous pemphigoid steroids and tetracyclines (blister) trail. The British Journal of Dermatology. 2015;**173**:227-234. DOI: 10.1111/bjd.13729

[89] de Vega IF, Iranzo-Fernández P, Mascaró-Galy JM. Bullous pemphigoid: Clinical practice guidelines. Actas Dermo-Sifiliográficas. 2014;**105**:328-346. DOI: 10.1016/j.ad.2012.10.022

[90] Schmidt E, Zillikens D. The diagnosis and treatment of autoimmune blistering skin diseases. Deutsches Ärzteblatt International. 2011;**108**:399-405. DOI: 10.3238/arztebl.2011.0405

[91] Tirado-Sanchez A, Diaz-Molina V, Ponce-Olivera RM. Efficacy and safety of azathioprine and dapsone as an adjuvant in the treatment of bullous pemphigoid. Allergologia et Immunopathologia. 2012;**40**:152-155. DOI: 10.1016/j.aller.2010.12.009

[92] Sticherling M, Franke A, Aberer E, Gläser R, Hertl M, Pfeiffer C, Rzany B, Schneider S, Shimanovich I, Werfel T, Wilczek A, Zillikens D, Schmidt E. An open, multicenter, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone. The British Journal of Dermatology. 2017;**117**:1299-1305. DOI: 10.1111/bjd.15649

[93] Kwarta SG, Jorizzo JL. Bullous pemphigoid: A case series with emphasis on long-term remission off therapy. Journal of Dermatological Treatment. 2013;**24**:327-331. DOI: 10.3109/09546634.2012.660519

[94] Du-Thanh A, Merlet S, Maillard H, Bernard P, Joly P, Esteve E, Richard MA, Pauwels C, Ingen-Housz-Oro S, Guillot B, Dereure O. Combined treatment with low-dose methotrexate and initial short-term superpotent topical steroids in bullous pemphigoid: An open, multicetre, retrospective study. The British Journal of Dermatology. 2011;**165**:1337-1343. DOI: 10.1111/j.1365-2133.2011.10531.x

[95] Shetty S, Ahmed AR. Treatment of bullous pemphigoid with rituximab: Critical analysis of the current literature. Journal of Drugs in Dermatology. 2013;**12**:672-677 23839185

[96] Ahmed AR, Shetty S, Kaveri S, Spigelman ZS. Treatment of recalcitrant bullous pemphigoid (BP) with a novel protocol: A retrospective study with a 6-year follow-up.

Journal of the American Academy of Dermatology. 2016;**74**:700-708.e3. DOI: 10.1016/j.jaad.2015.11.030

[97] London VA, Kim GH, Fairley JA, Woodley DT. Successful treatment of bullous pemphigoid with omalizumab. Archives of Dermatology. 2012;**148**:1241-1243. DOI: 10.1001/archdermatol.2012.1604

[98] Herrero-Gonzalez JE, Sitaru C, Klinker E, Bröcker EB, Zillikens D. Successful adjuvant treatment of severe bullous pemphigoid by tryptophan immunoadsorption. Clinical and Experimental Dermatology. 2005;**30**:519-522. DOI: 10.1111/j.1365-2230.2005.01853.x

[99] Chi CC, Wang SH, Charles-Holmes R, Ambros-Rudolph C, Powell J, Jenkins R, Black M, Wojnarowska F. Pemphigoid gestationis: Early onset and blister formation are associated with adverse pregnancy outcomes. The British Journal of Dermatology. 2009;**160**:1222-1228. DOI: 10.1111/j.1365-2133.2009.09086.x

[100] Lipozencic J, Ljubojevic S, Bukvic-Mokos Z. Pemphigoid gestationis. Clinics in Dermatology. 2012;**30**:51-55. DOI: 10.1016/j.clindermatol.2011.03.009

[101] Semkova K, Black M. Pemphigoid gestationis: Current insights into pathogenesis and treatment. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2009; **145**:138-144. DOI: 10.1016/j.ejogrb.2009.05.012

[102] Jackson S, Gilchrist H, Nesbitt LT. Update on the dermatologic use of systemic glucocorticosteroids. Dermatologic Therapy. 2007;**20**:187-205. DOI: 10.1111/j.1529-8019.2007.00133.x

[103] Marker M, Derfler K, Monshi B, Rappersberger K. Successful immunoapheresis of bullous autoimmune diseases: Pemphigus vulgaris and pemphigoid gestationis. Journal der Deutschen Dermatologischen Gesellschaft. 2011;**9**:27-31. DOI: 10.1111/j.1610-0387.2010.07500.x

[104] Shan XF, Zhang FR, Tian HQ, Wang N, Zhou SJ, Wang GJ. A case of linear IgA dermatosis successfully treated with tetracycline and niacinamide. International Journal of Dermatology. 2016;**55**:e216-e217. DOI: 10.1111/ijd.12524

[105] Chan LS. Ocular and oral mucous membrane pemphigoid (cicatricial pemphigoid). Clinics in Dermatology. 2012;**30**:34-37. DOI: 10.1016/j.clindermatol.2011.03.007

[106] Sobolewska B, Deuter C, Zierhut M. Current medical treatment of ocular mucous membrane pemphigoid. The Ocular Surface. 2013;**11**:256-266. DOI: 10.1016/j.jtos.2013.02.003

[107] Nottage JM, Hammersmith KM, Murchison AP, Felipe AF, Penne R, Raber I. Treatment of mucous membrane pemphigoid with mycophenolate mofetil. Cornea. 2013;**32**:810-815. DOI: 10.1097/ICO.0b013e31826af7b8

[108] McCluskey P, Chang JH, Singh R, Wakefield D. Methotrexate therapy for ocular cicatricial pemphigoid. Ophthalmology. 2004;**111**:796-801. DOI: 10.1016/j.ophtha.2003.07.010

[109] Thorne JE, Woreta FA, Jabs DA, Anhlat GJ. Treatment of ocular mucous membrane pemphigoid with immunosuppressive drug therapy. Ophthalmology. 2008;**115**:2146-2152.e1. DOI: 10.1016/j.ophtha.2008.08.002

[110] Foster CS, Ahmed AR. Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid: A preliminary study. Ophthalmology. 1999;**106**:2136-2143. DOI: 10.1016/S0161-6420(99)90496-7

[111] You C, Lamba N, Lasave AF, Ma L, Diaz MH, Foster CS. Rituximab in the treatment of ocular cicatricial pemphigoid: A retrospective cohort study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2017;**255**:1221-1228. DOI: 10.1007/s00417-017-3603-3

[112] Kim JH, Kim SC. Epidermolysis bullosa acquisita. Journal of the European Academy of Dermatology and Venereology. 2013;**27**:1204-1213. DOI: 10.1111/jdv.12096

[113] Arora KP, Sachdeva B, Singh N, Battacharya SN. Remission of recalcitrant epidermolysis bullosa acquisita (EBA) with colchicine monotherapy. The Journal of Dermatology. 2005; **32**:114-119 PMID: 15906541

[114] Hoon J, Kim YH, Kim SC. Epidermolysis bullosa acquisita: A retrospective clinical analysis of 30 cases. Acta Dermato-Venereologica. 2011;**91**:307-312. DOI: 10.2340/0001 5555-1065

[115] Gürcan HM, Ahmed AR. Current concept in the treatment of epidermolysis bullosa acquisita. Expert Opinion on Pharmacotherapy. 2011;**12**:1259-1268. DOI: 10.1517/14656566.2011.549127

[116] Oktem A, Akay BN, Boyvat A, Kundakci N, Erdem C, Bostanci S, Sanli H, Kocyigit P. Long-term results of rituximab-intravenous immunoglobulin combination therapy in patients with epidermolysis bullosa acquisita resistant to conventional therapy. The Journal of Dermatological Treatment. 2017;**28**:50-54. DOI: 10.1080/09546634.2016.1179711

[117] Cardones AR, Hall RP. Management of dermatitis herpetiformis. Dermatologic Clinics. 2011;**29**:631-635. DOI: 10.1016/j.det.2011.06.015

[118] Pulido OM, Gillespie Z, Zarkadas M, Dubois S, Vavasour E, Rashid M, Switzer C, Godefroy SB. Introduction of oats in the diet of individuals with celiac disease. Advances in Food and Nutrition Research. 2009;**57**:235-285. DOI: 10.1016/S1043-4526(09)57006-4

[119] Fric P, Gabrovska D, Nevoral J. Celiac disease, gluten-free diet, and oats. Nutrition Reviews. 2001;**69**:107-115. DOI: 10.1111/j.1753-4887.2010.00368.x

[120] Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. Journal of Pediatric Gastroenterology and Nutrition. 2009;**48**:559-565. DOI: 10.1097/MPG.0b013e3181668635

[121] Willsteed E, Lee M, Wong LC, Cooper A. Sulfasalazine and dermatitis herpetiformis. The Australasian Journal of Dermatology. 2005;**46**:101-103. DOI: 10.1111/j.1440-0960.2005.00152.x

[122] Ujiie H, Aoyagi S, Horie K, Shimizu H. Cutaneous-type pemphigus vulgaris successfully treated with topical corticosteroids. The Journal of Dermatology. 2016;**43**:840-841. DOI: 10.1111/1346-8138.13271

[123] Dumas V, Roujeau JC, Wolkenstein P, Revuz J, Cosnes A. The treatment of mild pemphigus vulgaris and pemphigus foliaceus with topical corticosteroid. British Journal of Dermatology. 1999;**140**:1127-1129 PMID: 10354082

[124] Robinson JC, Lozada-Nur F, Frieden I. Oral pemphigus vulgaris. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 1997;**84**:349-355 PMID: 9347496

[125] Mignogna MD, Fortuna G, Leuci S, Adamo D, Dell'Aversana Orabona G, Ruoppo E. Adjuvant triamcinolone acetonide injections in oro-pharyngeal pemphigus vulgaris. Journal of the European Academy of Dermatology and Venereology. 2010;**24**:1157-1165. DOI: 10.1111/j.1468-3083.2010.03610.x

[126] Ruocco V, Ruocco E, Caccavale S, Gambardella A, Lo Schiavo A. Pemphigus vegetans of the folds (intertriginous areas). Clinics in Dermatology. 2015;**33**:471-476. DOI: 10.1016/j.clindermatol.2015.04.011

[127] Iraji F, Asilian A, Siadat AH. Pimecrolimus 1% cream in the treatment of cutaneous lesions of pemphigus vulgaris: A double-blind, placebo-controlled clinical trial. Journal of Drugs in Dermatology. 2010;**9**:684-686 PMID: 20645531

[128] Tabrizi MN, Chams-Davatchi C, Esmaeeli N, Noormohammadpoor P, Safar F, Etemadzadeh H, Ettehadi HA, Gorouhi F. Accelerating effects of epidermal growth factor on skin lesions of pemphigus vulgaris: A double-blind, randomized, controlled trial. Journal of the European Academy of Dermatology and Venereology. 2007;**21**:79-84. DOI: 10.1111/j.1468-3083.2006.01873.x

[129] Iraji F, Banan L. The efficacy of nicotinamide gel 4% as an adjuvant therapy in the treatment of cutaneous erosions of pemphigus vulgaris. Dermatologic Therapy. 2010; **23**:308-311. DOI: 10.1111/j.1529-8019.2010.01329.x

Chapter 9

Wound Care in Immunobullous Disease

Emily Nadelmann and Annette Czernik

Additional information is available at the end of the chapter

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Abstract

The chapter introduces the steps to achieving proper wound care in immunobullous disease. It describes the clinical characteristics and nature of "wounds" formed in pemphigus versus pemphigoid diseases. Namely, pemphigus diseases typically result in acantholysis in the epidermis and the formation of flaccid blisters. In contrast, bullous pemphigoid presents with basal keratinocyte hemidesmosomes in the dermoepidermal junction, which results in a split at the dermoepidermal junction and clinically forms tense blisters. Therefore, there is a separate protocol for treating the wounds in each of these diseases, which must take additional patient specific factors into consideration.

Keywords: wound, care, wound healing, wound dressing, immunobullous disease, bullous pemphigoid, pemphigus vulgaris, immunosuppressant

1. Introduction

Patients suffering from immunobullous disease have open wounds with a tendency to develop new blisters, which presents a unique problem when addressing wound care. These patients also have fragile skin limiting the use of adhesives. Immunosuppressant treatments increase infection risk and also prednisone slows wound healing but is needed to treat the disease. Therefore, there are many complexities surrounding proper wound care specific to these patients.

Clinical experience has shaped the steps to achieving wound care in immunobullous disease, but more research must be conducted to determine the best wound dressings for this critical patient population. While there are many similarities in the wound care of the pemphigus versus pemphigoid family, the differences in the nature of wounds formed in each of these diseases, calls for a unique plan.

2. Introduction to pemphigus

Pemphigus is a group of autoimmune blistering diseases of both the skin and mucosa, which is caused by the loss of cell to cell adhesion of keratinocytes which leads to intraepidermal blisters [1].

The classic forms are pemphigus vulgaris and pemphigus foliaceus. Pemphigus vulgaris most frequently presents with mucous membrane erosions (see **Figure 1**). Additionally, more than half of the patient population will also have cutaneous blisters and erosions. These blisters form in the deeper portion of the epidermis, directly above the basal cell layer. Pemphigus vegetans is a variant of pemphigus vulgaris that occurs as a result of polymicrobial superinfection of lesions [2].

In contrast, patients with pemphigus foliaceus only have cutaneous involvement, and lack mucosal lesions. The splits occur in the superficial part of the epidermis, mostly in the granular layer. Pemphigus erythematosus and fogo selvagem are localized and endemic variants of pemphigus foliaceus [3].

Paraneoplastic pemphigus was recently recognized as a disease distinct from the classic forms of pemphigus. These patients have a known or occult neoplasm, commonly of lymphoid tissue. Paraneoplastic pemphigus also features painful, severe oral and often conjunctival erosions [1].

Aside from the three classical cases are other less prevalent versions. IgA pemphigus is characterized by IgA (as opposed to IgG) autoantibodies directed against keratinocyte cell surfaces and can either be the intraepidermal neutrophilic type (IEN) which forms pustules throughout the entire epidermis, or the subcorneal pustular dermatosis (SPD) type, with pustules primarily in the upper epidermis [1].

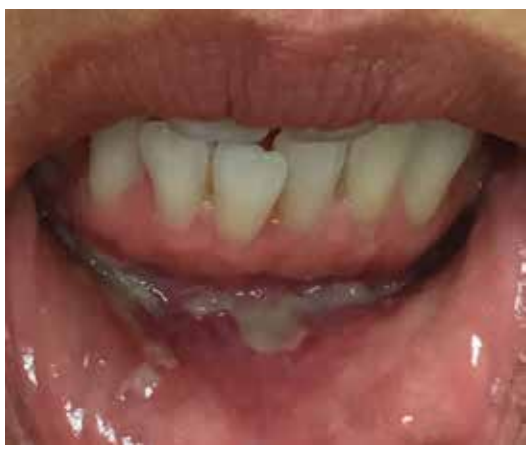

Figure 1. Patient with oral lesions in pemphigus vulgaris.

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3. Pathogenesis of pemphigus

All forms of pemphigus are a result of acantholysis, or the separation of keratinocytes from one another. The first step in this disease process is the dissolution of the intercellular substance, which leads to the separation of desmosomes. This results in the formation of a cleft within the epidermis, which expands to become bulla [1].

In every form of pemphigus, there are intercellular autoantibodies against keratinocyte cell-surface antigens, which are circulating and skin fixed. 80% of patients with active disease have circulating intercellular antibodies, and their titer usually correlates with disease activity. 90% of patients have tissue-fixed intercellular antibodies present in lesions and adjacent healthy skin. While the most prevalent antibodies are IgG, there are also frequently deposits of IgM, IgA and the complement protein C3. Since intercellular antibodies are uncommon when patients do not have pemphigus, they are very useful in making a diagnosis [1].

There is evidence that these intercellular antibodies are pathogenic. First of all, they are able to induce the histological changes of pemphigus (acantholysis) in organ cultures of human skin, and induce clinical and histologic lesions of pemphigus when passively administered to neonatal mice. Further studies reveal that placental transfer of maternal autoantibodies can induce transient lesions of the disease in newborn babies of women with active pemphigus vulgaris. Specifically absorbing out antibodies against desmoglein 1 or desmoglein 3 has been shown to prevent the passive transfer of disease in mice with pemphigus [4].

In pemphigus, the intercellular antibodies are directed against many keratinocyte cell-surface antigens, including desmoglein 1 and desmoglein 3. Both of these molecules are desmosomal transmembrane proteins in the cadherin family. The pathogenic antibodies against these proteins attack the portion of the protein that is expressed on the external surface of the cells and multiple epitopes on the same molecule can be targeted. In pemphigus vulgaris, intercellular antibodies are predominantly directed against desmoglein 3 and less often against desmoglein 1. However, in pemphigus foliaceus, the antibodies are mostly directed against desmoglein 1. Serological analysis has proposed that antibodies are also directed to other antigens, which was confirmed when pemphigus like lesions were induced in mice given intercellular antibodies not directed against desmoglein 1 or 3 [5]. It was observed that these additional antigens included acetylcholine receptors on keratinocytes.

Additionally, the subclass of the antibody response seems to dictate whether intercellular antibodies cause clinical disease. While IgG1 antibodies against desmoglein 3 are present in equal frequency in individuals with or without pemphigus vulgaris, IgG4 antibodies are almost exclusively present in patients with active disease [4]. Similarly, IgG1 antibodies against desmoglein are present in both individuals with or without endemic pemphigus and with or without active. It is believed that in endemic pemphigus, an unknown environmental agent might trigger the production of non-pathogenic IgG1 antibodies against desmoglein 1. However, the appearance of a clinical disease might be triggered by the presence of an HLA susceptibility gene required for the production of a pathogenic IgG4 response [4].

The exact process by which intercellular antibodies cause loss of cellular adhesion is not yet elucidated, though it does seem that the subclass of IgG response plays a role. There are various theories surrounding the exact mechanism. It is possible that the antibodies either physically block adhesion sites on desmoglein or on other adhesion molecules, or maybe they interfere with their structure or other functions or with the assembly of desmosomes. It is also possible that the antibodies stimulate release of proteolytic enzymes. In staphylococcal scalded skin syndrome, which is caused by a toxin that binds to and cleaves desmoglein 1, patients form blisters similar to those caused by pemphigus foliaceus [6]. Finally, one last possibility of the mechanism is that the antibodies trigger a signaling event which leads to reorganization of the cytoskeleton of keratinocytes, and causes the affected cells to shrink, pull away, and separate from adjacent keratinocytes [6].

4. Introduction to pemphigoid

The pemphigoid group can be broken down into bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, as well as epidermolysis bullosa acquisita.

Bullous pemphigoid is the most prevalent subepidermal blistering disease of the skin. It is most common in the elderly and is correlated with significant morbidity. The typical presentation is a generalized bullous eruption (**Figure 2**), but it frequently varies in the early stages of the disease. In this disease, patients typically make autoantibodies against two components of hemidesmosomes, which are the junctional adhesion complexes found in skin.

Mucous membrane pemphigoid is a very rare autoimmune subepithelial blistering disorder that has several notable features. It typically involves the mucosae, follows a sustained course, and tends to scar the affected areas. This disorder is a "disease phenotype" that encompasses a heterogeneous group of blistering disease, which tend to affect mucosal surfaces. Most patients

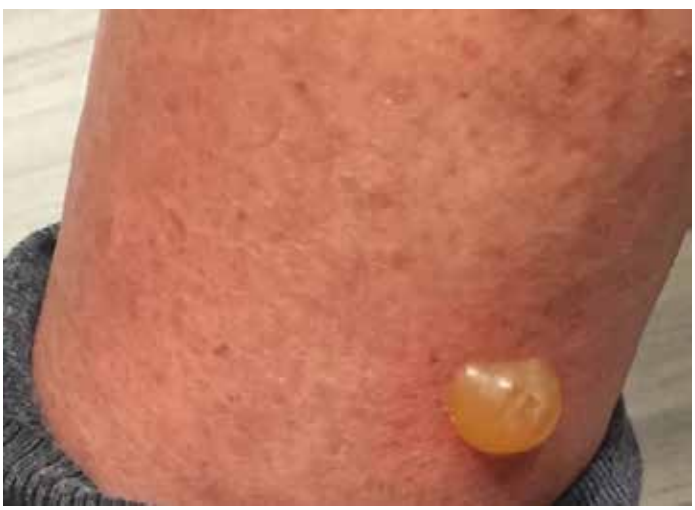

Figure 2. Patient with bullous pemphigoid with intact bulla on lower leg.

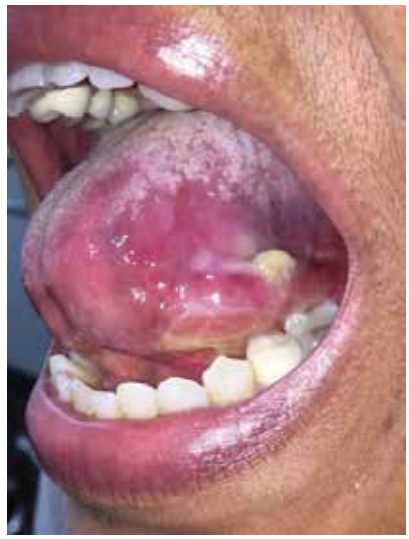

Figure 3. Patient with epidermolysis bullosa acquisita with mucosal lesion.

have linear deposits of immunoglobulins and/or complement components along the epithelial basement membrane zone of the skin and mucosae. There are classically low levels of circulating anti-basement membrane autoantibodies detected in the serum of some patients, at a low titer. This disease is recurrent and progressive and can have serious complications. If atrophic scarring and fibrosis affect the conjunctivae, it can ultimately lead to blindness [7].

Epidermolysis bullosa acquisita (EBA) is also a very rare disease. It is an acquired subepidermal bullous disease in which the patient has autoimmunity to type VIII collagen, which is the major component of the anchoring fibrils of the dermal-epidermal junction. Patients vary in the clinical presentation of this disease; some patients have a mechanobullous disorder that resembles dystrophic epidermolysis bullosa, while others have symptoms similar to bullous pemphigoid or mucous membrane pemphigoid [8] (**Figure 3**).

5. Pathogenesis of pemphigoid family

Bullous pemphigoid is immune-mediated and linked to a humoral and cellular response directed against two isolated self-antigens: BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e). BP antigen 180 is a transmembrane protein with a large collagenous extracellular domain. BP 230 is a cytoplasmic protein that is a member of the plakin family. Both of these antigens are components of hemidesmosomes, which are critical for epithelial-stromal adhesion in stratified and other complex epithelia [1].

Mucous membrane pemphigoid presents with mucocutaneous lesions, which are believed to be a result of when autoantibodies bind to the basement membrane zone of stratified epithelia of mucosa and skin. These autoantibodies bind to extracellular antigenic sites located within the anchoring filament zone, rather than within the hemidesmosomal plaque. However, the exact

Autoantigens	Location
BPAg2 (BP180)	Hemidesmosome/Lamina lucida (transmembrane)
BPAg1 (BP230)	Hemidesmosome (intracellular)
Integrin subunits α6/β4	Hemidesmosome (transmembrane)
Laminin-5 (laminin-332/epiligrin, α-3, β-3, γ-2 chains)	Lower lamina lucida
Laminin-6	Lower lamina lucida
Type VII collagen	Lamina densa/Sub-lamina densa

Table 1. Autoantigen in bullous pemphigoid, mucous membrane pemphigoid & epidermolysis bullosa acquisita and their localization within the dermis/epidermis junction (DEJ).

pathogenicity of autoantibodies involved in this disease has not been fully elucidated. In some patients with mucous membrane pemphigoid, NC16A domain-specific T cells were identified. Additionally, it was found that when patients have ocular disease, there is increased expression of collagen-binding heat shock protein 47 (HSP47) and TGF-B1 by conjunctival fibroblasts that might be associated with conjunctival scarring [7]. There are four subgroups of mucous membrane pemphigoid patients, based on the reactivity profile of patients' autoantibodies (**Table 1**).

Epidermolysis bullosa acquisita is also an immune-mediated disease. These patients have tissue-bound and circulating autoantibodies to a structural component of the dermal-epidermal junction. There is tissue injury where these antibody–antigen complexes are found. The role of these autoantibodies in causing disease has been reaffirmed by in vitro and in vivo animal models of the disease [8].

6. Wounds

6.1. Wounds in pemphigus vulgaris

Pemphigus vulgaris typically presents with painful, non-healing ulcerations in the mouth. These blisters rupture soon after forming and leave an ulcerated area. There are usually many ulcerations that are superficial and irregular in shape, which arise from mucosa of healthy appearance. The lesions most commonly form on the buccal and labial mucosa, the palate and the tongue. However, it is possible for any mucosal surface to be involved. In contrast to the oral lesions of aphthous stomatitis or viral infections that heal in a matter of days or weeks, these ulcerations usually will not heal on their own [9].

Due to the rarity of the disease, there is on average a 10-month delay in diagnosis and pemphigus only considered when lesions have remained for weeks to months, in spite of antibiotic, antifungal or antiviral therapy [10]. If there are multiple, non-healing oral ulcers that persist for longer than a month, pemphigus should be considered.

As the disease progresses over the following weeks to months, lesions begin to appear on the skin and with symptoms signifying nasal and esophageal involvement. Sometimes, the disease begins to manifest with skin lesions. The skin lesions begin as small blisters that are filled with

a clear fluid that arises from seemingly normal skin. The blisters are usually flaccid, since the overlying epidermis is thin and cannot sustain much pressure. Since the blisters are so fragile, they usually rupture in several days and form coin sized erosions often with a collarette of epidermis. The lesions are most frequently found on the scalp, upper chest and back. They are more commonly found on the medial or central part of the torso rather than the sides. The face and neck are also commonly involved, but lesions can appear on any surface covered by stratified squamous epithelium. It is important to also check the per inguinal areas, the pharynx and larynx, manifested by nasal congestion and morning mucous discharge. A recent systematic study showed that 49% of patients had symptoms of laryngeal or nasal involvement, or both [11].

If the lesions are left untreated, the bullae and erosions spread. As with burns, widespread lesions can be complicated by severe infection or metabolic disturbance, or both, leading to death. Prior to the development of systemic corticosteroids, about 75% of patients who develops pemphigus vulgaris died within a year [11]. However, improved diagnostic techniques now permit the recognition of subtler forms of disease. The severity of pemphigus can vary widely. There are milder forms that regress spontaneously and the progression of even the most severe forms can almost always be reversed with appropriate treatment.

Following treatment, lesions heal with crusting followed by reepithelization. While there is no scarring, there can be residual hyperpigmentation at sites of former lesions. The hyperpigmentation will usually disappear over several months. At some point, these patients can enter a phase of partial or complete remission. In partial remission, they can be maintained, lesion-free with minimum (<15 mg per day prednisone) doses of corticosteroids. In complete remission, they are lesion free for 2 months and do not need any therapy [9].

A longitudinal study was performed, which assessed the outcome of 40 patients. It showed that half of the patients reached complete and long-lasting remission after 5 years and three quarters reached the same end point after 10 years [9].

Despite the complete or partial remission, it is fairly typical for flares of disease activity to occur. The flare can present with new lesions and itching. There are many factors that are thought to possibly trigger a flare, including arthropod bites, hospitalization, dental work, exposure to the sun, cutaneous trauma, infection, as well as other forms of physical or emotional stress [9].

The wounds in pemphigus vegetans are very similar to pemphigus vulgaris, however, healing is accompanied by vegetating proliferation of the epidermis. The lesions present in intertriginous areas of the skin, including the axilla of the arm, the groin and the inframammary area and scalp. Due to the nature of the location of these lesions, they are often secondarily infected, which further slows the healing.

6.2. Pemphigus foliaceus

The wounds in the superficial forms of pemphigus differ greatly from those in pemphigus vulgaris. These diseases present in such a superficial layer of the skin, that there is not enough tissue to trap fluid and allow for blister formation. The lesions present as many pruritic, crusted, coin-sized patches on the upper torso, face and scalp (**Figure 4**). The skin had previously been healthy and the lesions have been described as "cornflakes". These superficial crusts can be removed fairly easily, and will leave behind superficial erosions. If the lesions are not treated, they will

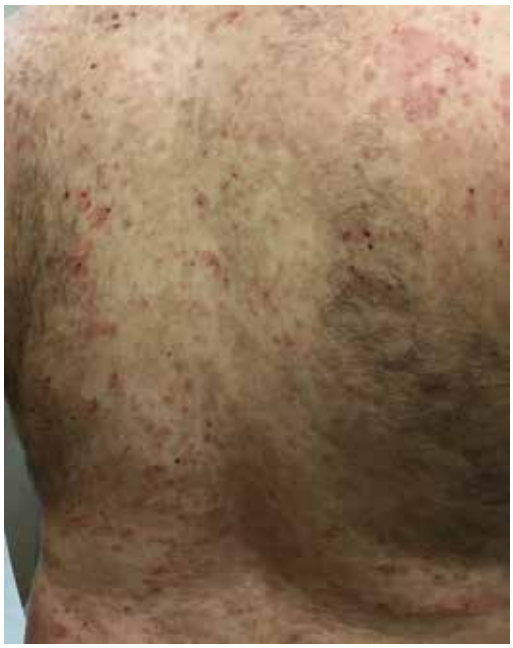

Figure 4. Patient suffering from pemphigus foliaceous on back.

not heal and will only increase in number. In more severe cases of superficial pemphigus, the lesions can appear to merge and present similarly to exfoliative erythroderma, where the entire skin surface is affected. Oral involvement is uncommon in superficial forms of pemphigus.

The two clinical variants of pemphigus foliaceus, pemphigus erythematosus and fogo selvagem also vary in their specific presentation. Pemphigus erythematosus tends to resemble lupus erythematosus in that it typically presents on the face in a butterfly distribution. In all forms of pemphigus, there are tissue-fixed intercellular deposits of antibodies. However, in pemphigus erythematosus, there are also often granular deposits of immunoglobulin or complement or both at the dermal-epidermal junction. As such, it is speculated that pemphigus erythematosus might be a crossover syndrome between pemphigus foliaceus and discoid lupus erythematosus. However, it is important to note that granular deposits of immunoglobulin or complement or both are not uncommon in normal sun exposed facial skin [1].

Fogo selvagem is histologically and immunologically identical to pemphigus foliaceus. The predominant difference is that it occurs in only certain rural areas in the world. Treatment for pemphigus foliaceus is similar to that for pemphigus vulgaris, requiring similar doses of drugs to control the disease. However, the prognosis is better for pemphigus foliaceus, due to the fact that the lesions are more superficial and there is therefore a smaller risk of infection, fluid loss and metabolic disturbance [1].

6.3. Wounds in bullous pemphigoid

Bullous pemphigoid has many different forms of its cutaneous presentation. There is a non-bullous, prodromal phase of the disease, the signs and symptoms are not always specific

to bullous pemphigoid. For example, there can be mild to severe intractable pruritus alone or in association with excoriated, eczematous, papular and/or urticarial lesions that may remain for several weeks or months. At this phase, the only sign of the disease may be these nonspecific cutaneous findings [12].

At the bullous stage of bullous pemphigoid, the patient develops vesicles and bullae on an urticarial base. They commonly also have urticarial and infiltrated papules and plaques, which can present in an annular or figurate pattern. Unlike in pemphigus, these blisters are tense. They range from 1 to 4 cm in diameter, are filled with a clear fluid and persist for several days (**Figure 2**). After they pop, they become eroded and crusted areas. Sometimes, the blister fluid becomes blood-tinged. Commonly, the lesions have symmetrical distribution patterns and they often present on the flexural aspects of the limbs and lower trunk, including the abdomen [12].

There are residual post inflammatory changes ranging from hyper- to hypopigmentation. Occasionally, milia appear as well (**Figure 6**). In 10–30% of patients, there is involvement of the oral cavity. Rarely, the mucosae of the eyes, nose, pharynx, esophagus and anogenital region are affected. Additionally, in about half of the patients, there is a peripheral blood eosinophilia.

6.4. Wounds in mucous membrane pemphigoid

The oral and conjunctival mucosae are the two most commonly involved sites for patients with this diagnosis. However, it is still possible for the disease to first appear in and affect any mucosal site, including the external genitalia, the anus, the upper aerodigestive tract and/or the esophagus. Around 85% of patients with mucosal membrane pemphigoid have oral involvement and it is possible that the oral cavity is the only site of disease activity [13].

Figure 5. Epidermolysis bullosa acquisita patient with post inflammatory hyperpigmentation in annular pattern on legs.

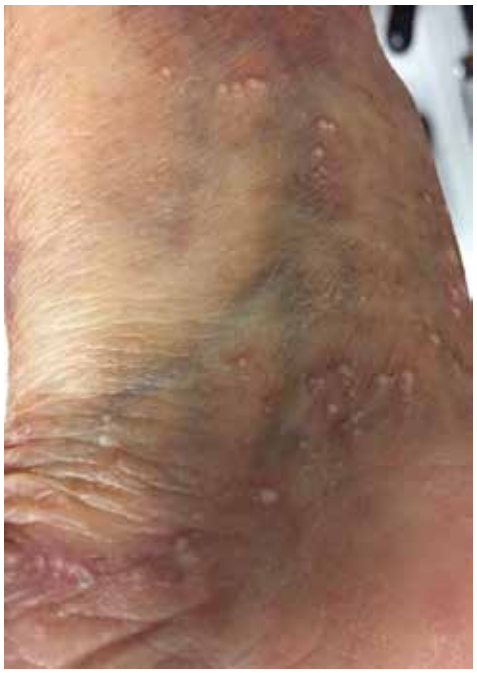

Figure 6. Patient with milia on wrist, following treatment for bullous pemphigoid.

Within the oral cavity, lesions often involve the gingiva, buccal mucosa, and palate. It is less common to see lesions on the alveolar ridges, the tongue and the lips [1] (**Figure 3**).

Frequently, mucous membrane pemphigoid in the oral cavity presents as desquamative gingivitis along with bleeding erosions and paresthesia. In this case, it is rare to see small intact blisters. Sometimes, periodontal ligament damage and the loss of teeth may occur as a result of chronic inflammation. In certain parts of the mouth, transient vesicles can lead to chronic erosions. This can occur on the palate and is accompanied with variable pain. When there are lesions on the tongue, they are found on the lateral and ventral surfaces. Adhesions may form in the area of the uvula and tonsillar fossae as well as between the tongue and the floor or the mouth. After the lesions heal, they may become white reticulated striations, which look similar to lichen planus [1].

When the conjunctiva is affected, this can lead to blindness. Often, the conjunctiva is the only site affected. In most cases, lesions occur in both eyes, although the disease can begin unilaterally as well.

At the start of ocular involvement, there is nonspecific, chronic conjunctivitis, with burning, soreness, foreign-body sensation or mucus production. This conjunctivitis can either go into remission or become exacerbated, where it will progress to subepithelial conjunctival fibrosis [1].

It is rare to see conjunctival vesicles or blisters on the tarsal conjunctiva. Chronic inflammation is detrimental to the eyes and can lead to progressive scar tissue formation, shortened inferior fornices, and symblepharon formation, which is adhesion between bulbar and palpebral conjunctival surfaces. Trichiasis, or inwardly angled eyelashes, and entropion, can also result

from conjunctival fibrosis. If the disease is not adequately controlled, trichiasis, entropion and xerosis (from scarring of lacrimal ducts) will lead to superficial corneal trauma, corneal neovascularization with subsequent corneal ulceration and blindness [7].

When the nasopharynx is involved, it is chronic and leads to extensive lesions of the upper aerodigestive tracts. The lesions lead to crusted ulcerations, epistaxis, fibrous adhesions between adjacent mucosal surfaces, and airway obstruction. When the pharynx is involved, there are typically ulcerations of the posterior or lateral pharynx and dysphagia. Laryngeal involvement is a potentially serious manifestation. It will present as hoarseness, loss of speech and can even lead to life-threatening stenosis, which requires tracheostomy [7].

While there is often dysphagia from the erosions of the esophageal mucosa, often esophageal disease can be asymptomatic. On the other hand, if there is chronic inflammation, it can lead to strictures and stenosis, with the associated dysphagia [7].

It is rare to see lesions on the genital and anal mucosa. However, when they appear, there are blisters and chronic erosions. In females, if there is progressive disease, it can lead to atrophic scarring and narrowing of the introitus. On the other hand, in male patients, adhesions can appear between the prepuce and the glans penis. When the anus is affected, it can result in anal scarring and in more severe cases, it can lead to stricture formation [7].

25–30% of patients with mucous membrane pemphigoid have skin involvement [7]. In this case, the lesions typically appear on the scalp, face, neck and upper trunk. These lesions differ from bullous pemphigoid in that they present as erythematous plaques, which lead to recurrent blister formation and erosions, with subsequent atrophic scarring. There are typically not too many lesions, but on occasion a patient can have bullous pemphigoid like clinical presentation [14].

In the Brunsting-Perry variant, skin lesions are only found on the head and neck region and mucosal involvement is typically minimal or absent. When the skin lesions are on the scalp, it can lead to scarring alopecia [33].

6.5. Wounds in epidermolysis bullosa acquisita

The presentation of epidermolysis bullosa acquisita is typical for a non-inflammatory mechanobullous disease. Namely, these patients develop acral blisters that heal with atrophic scarring, milia and hyper or hypopigmentation (**Figure 5**). Cutaneous blisters and subsequent erosions appear within non-inflamed skin or on areas of scarring. They are more frequently serous, but can also be hemorrhagic. They are typically found in more trauma-prone surfaces, including the elbows, knees and dorsal aspects of the hands, feet, and toes. Up to 20% of patients do have scalp involvement and extensive non-healing erosions with scarring alopecia have been noted in some cases [1].

6.6. General principles of wound care

Wound healing is a complex and active process that follows three consecutive phases. These include inflammation, tissue formation and tissue remodeling. In order for wound healing to be effective, there must be synchronization of not only cell–cell and cell-matrix interactions, but also interplay of cytokines to ensure successful communication among various processes.

The major players in this process include extracellular matrix proteins, cell surface receptors or integrins and growth factors. The extracellular matrix proteins have many functions, and bind directly to the cell surface receptors. As a result, they determine the effects of growth factors, such as TGF-beta, on cells [1].

While injured fetal tissue has the capacity to regenerate, or heal completely without fibrosis, injured tissue in children and adults still follows a reparative process, but can lead to fibrosis. There are many systemic diseases, including diabetes mellitus and atherosclerosis, as well as more local factors, such as pressure and infection, that can lead to chronic non-healing wounds [4].

When an injury occurs, it is critical to restore skin integrity and homeostasis. Therefore, the main goal of wound healing response is to quickly reform a functional skin barrier. The best wound healing response would be if there was complete regeneration of skin tissue and its adnexal structures. Ideally, original skin function and morphology would be completely restored. However, this is often not the final result of wound repair and there are variable responses in how skin tissue reforms [4].

6.7. Regeneration versus repair

In wound healing response, a distinction must be made between regeneration and repair. The wound healing responses follows repair more than regeneration. In other words, the skin barrier is not restored to its pre-injured state, but rather leads to fibrosis or scar formation. Additionally, adnexal structures, including hair follicles, sweat and sebaceous glands, and components of the dermal extracellular matrix may not regenerate. As a result, there is a loss of normal skin function and impaired morphology [15].

Regeneration can occur during embryogenesis to injured fetal skin. It is able to heal completely without fibrosis. Research has indicated that fibromodulin, a small leucine rich proteoglycan, is thought to mediate scarless fetal skin wound repair [15]. It is thought that this process partly works via transforming-growth factor- beta modulation. A research study showed that when fibromodulin−/− mice were compared to wild type mice, they were found to have delayed wound closure and a large increase in scar size. When they were later administered exogenous fibromodulin, there was improvement in wound closure and scar size [15].

6.8. Effect of immune response on wound healing

The immune system, and its major players, including neutrophils and macrophages hold a key role in wound healing. Inflammation influences the repair process and can affect the quality of the wound and the extent of scarring. Many repair models have shown that there is an inverse correlation between the strength of the inflammatory response and the ability to undergo regeneration. Namely, it appears that when the inflammatory immune response is greater, there is more inappropriate wound repair [16].

6.9. Insights from animals on the immune system and wound healing

Amphibians and fish are unique in their ability to regenerate anatomically complete and fully functional tissues and organs. Specifically, urodele amphibians (newts and salamanders) can regenerate a range of organs and tissues [17]. This occurs in a process in which there is dedifferentiation of cells at the site of amputation injury, followed by their proliferation to produce a blastemal that finally reforms the missing tissue. It is postulated that the ability to regenerate is related to the fact that the regenerative response induces minimal inflammation. However, further investigation is needed to elucidate the role of inflammation in the regenerative response [1].

Furthermore, zebrafish are able to regenerate their entire caudal fin, even as adults, including the original pigment and color structures [18]. However, in this process, regeneration occurs in the presence of inflammation since there is an infiltration of myeloid inflammatory cells early on. When an experiment knocked out the gene responsible for myeloid cell development and the inflammatory response, there was no effect on fin regeneration [19]. Therefore, future research must examine whether there is a relationship between fin regeneration in zebrafish and the inflammatory response.

In mammals, such as mice and humans, the effects of inflammation on regeneration and repair have also been studied. In children and adults, wound repair results in scar formation. However, injured fetal skin is able to fully regenerate in a scarless manner [20]. It is noted that a major difference between fetal and post-natal skin is that there is a lack of significant inflammation in fetal skin post injury. Additionally, there is a difference in the extracellular matrix, cellular mediators, gene expression profiles as revealed by transplantation experiments, as well as unknown factors intrinsic to fetal skin [21].

There have been experiments using transgenic mice to learn more about wound healing. When mice were lacking nidogen 1, a basement membrane component, or TGF-beta, there was delayed wound healing [22]. Additionally, there was delayed wound healing in mice with a fibroblast-specific deletion of integrin B1, which binds extracellular matrix proteins, in mice that lack superoxide dismutase, an important ant oxidative enzyme, or IL-6 in mice that lack Toll-like Receptor 3, and have a defective recruitment of neutrophils and macrophages [23]. When mice lack matrix metalloproteinases, which degrade extracellular matrix proteins, or when mice are deficient in Natural Killer (NK) or T Cells, there is accelerated wound healing [24].

6.10. Wound depth and wound healing

Different terminology is used to describe a wound, depending on its depth. Wounds are categorized as erosions when they only affect the epidermis. However, when the wound extends into the dermis, it is referred to as ulceration. Partial thickness wounds are when the epidermis and portions of the dermis are missing, and the ulcer extends into the mid dermis. In partial thickness wounds, adnexal structures remain. On the other hand, in full thickness wounds, the entire dermis is involved, and the wound extends into the subcutaneous fat. In these wounds, adnexal structures are lost as a source of keratinocytes necessary for reepithelization [1].

The extent to which the skin can repair or regenerate is dependent on the depth of the skin injury. For example, erosions are the least severe of the wounds mentioned above. When they heal, the entire epidermis is able to regenerate, and here is no scarring. On the other hand, ulcerations heal via a reparative, not a regenerative process, and are therefore associated with scar formation [1].

As mentioned above, in partial-thickness wounds, the preserved adnexal structures serve as a source of epithelial to repopulate the epidermis [25]. Specifically, epithelia from these structures and the wound edge migrate across the wound surface to provide full coverage.

However, in full thickness wounds, where adnexal structures are lost, the reepithelialization can only occur from the wound edges [26]. As a result, healing of full-thickness wounds includes contraction. While the mechanism of contraction in wound healing is not fully elucidated, it is believed that contraction may be mediated by mechanical or biologic factors, such as differentiation of fibroblasts into myofibroblasts. During contraction, there is centripetal movement of pre-existing tissue, rather than formation of new tissue.

6.11. Cellular and molecular aspects of skin repair

Numerous cell types interact during the repair response. These include cells that reside in the tissues, such as keratinocytes, endothelial cells, and fibroblasts, as well as hematopoietic cells that are recruited to the site of tissue damage. These cell types all interact during the three phases of wound repair [27].

6.12. Inflammatory phase

The first phase of wound repair is the hemostasis and inflammatory phase. When tissue injury occurs, there is extravasation of blood into the wound and eventual clot formation. The clot is comprised of collagen, platelets, thrombin and fibronectin. These factors release cytokines and growth factors that initiate the immune response [28].

Then, there is local activation of innate immune functions and chemoattraction. Both of these processes result in an early influx of polymorphonuclear leukocytes or neutrophils. Neutrophils destroy bacteria by releasing caustic proteolytic enzymes. Next, there is an invasion of blood monocytes, which differentiate into tissue macrophages. Activated macrophages clear the wound of dead neutrophils, bacteria and debris, as well as release many cytokines necessary for angiogenesis, such as VEGF, TGF-Beta, and platelet derived growth factor. As inflammation progresses, the number of neutrophils decline, while the number of macrophages increase [28].

6.13. Proliferative phase

The release of cytokines and growth factors is necessary for the initiation of the proliferative phase. In this phase, invading macrophages, fibroblasts and endothelial cells make up newly formed granulation tissue. Many proteins such as fibrin, fibronectin, vitronectin, collagen III and tenascin are components of the provisional extracellular wound matrix which enable cell

adhesion, migration and proliferation. There are also epidermal-mesenchymal interactions at the wound edge, which stimulate keratinocyte proliferation and migration, and ultimately lead to reepithelization [29].

6.14. Remodeling (maturation) phase

After epithelization is complete and cell proliferation and neovascularization stop, scar tissue forms and the wound enters the remodeling phase. This phase lasts several months and is described by a balance between the synthesis of new components of scar matrix and their degradation by proteases. The degree of balance between the two processes determines whether there is normal or abnormal scar formation. Abnormal scar formation includes atrophic scars, hypertrophic scars and keloids. The exact mechanism of how granulation tissue regresses and transforms into scar tissue is still not completely known [30].

In addition to the scar tissue formation, there is also regression of vascular structures, transformation of fibroblasts into myofibroblasts, substitution of provisional extracellular matrix with a permanent collagenous matrix and a final act of the inflammatory response. The exact mechanism of this step is still not known [31].

6.15. Wound healing and aging

There are two main mechanisms which are related to human aging. These include telomere shortening and DNA damage. When telomere shortening or dysfunction occurs, there is instability of chromosomes. In a study examining telomerase-deficient mice, impaired wound healing was noted. Additionally, when mice had increased activation of the transcription factor p53 within the epidermis, they developed an early aging phenotype of their skin and impaired wound healing [32].

6.16. Wound healing and immunosuppressants

Immunosuppressive therapy is used to treat immunobullous disease. Depending on the specific immunosuppressive treatment, wound healing is affected to different degrees.

Wound healing is a complicated process involving many different cells, hormones, cytokines, proteases and growth factors. Additionally, these can be broken into four phases: hemostasis, inflammation, proliferation and remodeling, which are each essential for adequate wound are healing. Research demonstrates that immunosuppressive agents that are used in conditions such as organ transplant and IBD have been shown to impair the wound healing process [33] (**Table 2**).

6.17. Several inflammatory mediators involved in the wound healing process are affected

Immunosuppressants affect several inflammatory mediators involved in the wound-healing process. These include IL-2, IL-4, IFN-gamma, TNF, alpha, and GM-CSF. At the outset, IL-2 activates macrophages, T cells, NK cells and lymphokine-activated B cells and T cells. IL-4

Author(s)	Drug(s) under investigation	Type of study	Type of wound examined	Result
Burgos et al. [34]	Cyclosporine, tacrolimus, MMF, SLR, everolimus, prednisolone (in different combinations)	Retrospective	Abdominal wounds	Tacrolimus less likely to cause collections or bleeding ($p < 0.05$ and $p = 0.02$) Lymphocoeles more common in mammalian target of rapamycin-inhibitor regimens ($p = 0.012$)
Valente et al. [35]	MMF, SLR	Retrospective	Abdominal wounds	Incidence of wound complications 2.4% (MMF group) compared with 43.2% (SLR group) ($p < 0.0001$)
Grim et al. [27]	SLR, MMF, steroid and tacrolimus (in different regimens)	Retrospective	Abdominal wounds	31.8% in the SLR group developed wound complications compared with 14.3% in the tacrolimus group ($p = 0.0163$)
Selman et al. [36]	Rituximab	Prospective	A linear dorsal incision in mice	The results yield that the wound healing significantly decreased ($p < 0.05$) in Groups 2 and 3, which received Rituximab, as compared to control group.

Table 2. Role of immunosuppressive drugs in wound healing.

stimulates fibroblast proliferation early in the wound healing process and later on downregulates cytokine expression. IFN-gamma and TNF-alpha are both leukocyte chemoattractants. In addition, IFN gamma, along with GM-CSF, is a leukocyte activator [33].

6.18. Modes of action of immunosuppressant drugs

6.18.1. Systemic steroids

Systemic steroids are chemical modifications of natural glucocorticoids. The most commonly used systemic steroids include prednisone and prednisolone. To become active, prednisone is converted to prednisolone by modifying the 11-keto group to become an 11-hydroxyl group. The glucocorticoid activity of prednisone and prednisolone is 3–4 fold greater than hydrocortisone. Corticosteroids alter lymphocyte recirculation and create a transient lymphocytopenia. They also induce lymphocyte death. The most important immunosuppressive effect of corticosteroids is inhibiting cytokines, which further prevents T cell activation [37].

6.18.2. Azathioprine

Azathioprine is the 1-methyl-4-nitro-5-imidazolyl derivative of 6-MP. AZA and is metabolites suppress intracellular inosinic acid synthesis, which interferes with intracellular purine synthesis. This drug leads to a reduction in the number of circulating B and T lymphocytes, which results in decreased immunoglobulin production and reduced IL-2 secretion [33].

Stolzenburg et al. studied the effect of Azathioprine on anastomotic healing in rats. There were 48 Wilstar rats divided into groups of four per cage, then randomized into three groups receiving one daily dose of placebo, low dose, Azathioprine, and high dose Azathioprine. There were no significant differences in wound healing between the three groups [33].

6.18.3. Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an ester of an old drug, mycophenolic acid. It is an antimetabolite agent that interrupts purine metabolism in T and B lymphocytes. It inhibits the generation of cytotoxic T cells and the rejection of allogeneic cells. Research has shown that it can suppress the formation of antibodies against alloantigens in a chronic rejection model and that it can abolish the formation of antibodies against xenogeneic cells [33].

There have been some animal studies performed to look into the effect of mycophenolate mofetil on the healing of left-sided colon anastomosis in Sprague-Dawley rats. This study showed that MMF inhibits injury induced reparative proliferation of colonic mucosal cells. The bioavailability of MMF in humans is nearly 100% and pharmacokinetic measures are similar in humans and rats [33].

6.18.4. Rituximab and wound healing

Rituximab binds to the CD20 antigen found on the surface of all B-lymphocytes, it lyses the cells and activates complement. In all cases in which rituximab is given, there is a rapid decrease of circulating B-cells. B-cell recovery does not begin until 6–9 months after completion of treatment [38].

Rituximab delays wound healing in male mice and that further research is needed to study the direct effects of the drug on wound healing in humans [38].

There is a clear correlation between immunosuppressive agents, inflammatory mediators and the wound-healing process. This complicates treatment of autoimmune bullous diseases where immunosuppressant therapy is required to treat the underlying condition [33].

7. Wound dressings

Currently, there are many different wound dressings available. However, the specific type of dressing depends on characteristics of the wound. While clinical trials have examined the efficacy of different dressings for a variety of wounds, clinical experience has ultimately shaped most of the recommendations.

The commonly accepted mechanism of action of wound dressings is to support wound healing by acting as a barrier between the wound and the environment, by preventing drying of the tissue or autolytic debridement. There are some dressings which actually interfere with cellular and molecular mechanisms of the wound microenvironment, and counteract mechanisms that are considered incompatible with wound repair [39].

8. Role of growth factors

Growth factors help to regulate cell function during wound repair. Therefore, topical application of many growth factors can modify and even accelerate wound repair.

Platelet-derived growth factor (PDGF-BB) is the first and only recombinant growth factor to be effective and approved for the topical treatment of diabetic foot ulcers [40]. Currently, there is promise in the use of perilesional injections of granulocyte-macrophage colony-stimulating factor (GM-CSF). Wankell et al. showed that in transgenic mice, where an antagonist of GM-CSF was overexpressed in the epidermis, delayed wound healing was observed [41]. However, further studies must be conducted to further explore the efficacy of this treatment.

There is promise in a combined molecular and genetic approach. Ideally, genetically modified cells would synthesize and deliver the desired growth factor in a time-regulated and locally restricted manner to the wound site. This would overcome some of the limitations that are faced in the local application of recombinant growth factors [42].

9. Composition of a dressing

The exact composition of a dressing is an important factor in the decision process. It should be made of an inert material, which will not shed fibers or compounds into the wound. If the material is not inert, a foreign body or irritant can enter the wound and lead to an immune response.

A critical aspect of a wound dressing is the capacity to maintain a moist environment. Moisture assists the reparative process, by suppressing tissue desiccation and crust formation. If a wound is left to dry, a scab or eschar will form. This specifically occurs in the superficial dermis, which actually becomes integrated into the scab itself [1].

In 1962, there was a study conducted by George Winter that looked at moist wound healing. It demonstrated a 30% greater benefit of occlusive dressings versus air drying of wounds. There have been subsequent studies since Winter's work that further demonstrate the benefit of moist wound healing by occlusive dressings [31].

Winter and Scales conducted studies examining the effects of leaving wounds uncovered. They found that air dried wounds developed thicker scabs and reepithelialized at a slower rate. This is due to the fact that when the wound is air dried, the regenerating epidermis must migrate deeper below the dry fibrous tissue to a region of moisture where live cells survive. It is only in such an environment where epidermal cells are able to move toward bridging the defect of the wound. The thickness of the wound correlates with the deepness of the migration of the regenerating epidermis. The thickness of the wound in addition to the continuing loss of dermis and collagen and a reduction in adnexal structures, contributes to the depth of the scars and to a worse cosmetic outcome [31]. Therefore in the case of pemphigus and pemphigoid, the superficial depth lends itself to compute healing without scarring. The

predictable depth of these erosions is intraepidermal in the case of pemphigus vulgaris and at the dermis epidermal junction in bullous pemphigoid.

Furthermore, there are many endogenous factors that are essential for proper wound healing that are found in fluid from occluded acute cutaneous wounds that may be more available in a moist environment [31].

Finally, it is believed that moist wound healing environment has the ability to confer an electrical gradient between the wound and normal skin. Following injury of the skin, there is an internal battery and a current flow created until drying of the wound occurs. By maintaining the moisture, the electrical gradient may promote epidermal cell migration between the wound and the surrounding skin [39].

10. The role of oxygen in wound healing

The requirement for oxygen differs based on the stage of wound repair. Studies have shown that the oxygen requirement is low in the early wound repair stages. Following acute injury, there is a disruption of blood flow from clotting that prevents exsanguination. This leads to a temporary but extreme hypoxia, which is a signals the migration of keratinocytes and fibroblasts as well as the initiation of angiogenesis [43].

Additionally, studies have shown that hypoxia upregulates proliferation and production of TGF-Beta by dermal fibroblasts. Then, TGF-Beta stimulates production of extracellular matrix molecules. It is also noted that hypoxia allows keratinocytes to migrate better along keratin and fibronectin, and that low oxygen levels promote angiogenesis in the acute wound [43].

Therefore, the use of semipermeable dressings has been promoted to allow the appropriate oxygen tension for wound repair to proceed quickly. When acute wounds have been allowed to heal under occlusion, they have shown accelerated healing, greater resistance to breaking open, as well as better cosmetic outcomes than those that heal open to the air [44].

11. Traditional wound dressings

Traditionally, wound dressings have been composed of natural, synthetic or partially synthetic materials. Cotton, silk, linen or cellulose-based substances are naturally occurring materials that have been produced in many combinations to maximize clinical usefulness. Today, the basic cotton gauze dressing is composed of cotton plus cellulose acetate. The cellulose acetate is added to enhance the absorbency [1].

Different manufacturers incorporate various substances into the fabric. These include white petrolatum and other ointments, including paraffin wax (Vaseline gauze, aquaphor gauze), and can also include antibacterials such as povidone-iodine, sulfadiazine, bismuth, framycetin and chlorhexidine. Medicated dressings are frequently used for malodorous wounds such

as chronic ulcers, and are made of rayon, nylon or gauze. Activated charcoal cloth with or without antibacterial silver salt is also used for exudate absorption as well as odor control [1].

Traditional wound dressings are placed immediately against the wound bed and have multiple advantages. These include the advantage of having less chance of adhering to the wound. The main disadvantage of this type of dressing is the potential for maceration of the wound and surrounding skin if the dressing stays in place for an extended period of time [39].

While traditional dressings are relatively inexpensive and readily available, they require frequent replacement. This can be time consuming for both the patient and the medical staff. Therefore, traditional dressings are potentially costly in terms of the time required for healthcare personnel [44].

12. Technique for most conventional dressings

Currently, most dressings are layered and either qualifies as "pressure" or "non-pressure" dressings. A layered dressing is usually composed of three parts. There is a contact or interface layer, which is typically a non-adherent, fluid permeable material, which makes direct contact with the wound. Next, there is the absorbent layer. This is normally a cotton pad, gauze or other material. It is placed directly on top of the contact layer to "wick-in" and retain wound exudate. This also allows the dressing to mold to the shape of the wound. Finally, there is an outer layer or wrap, which is often tape or another banding material, such as a self-adhesive bandage. Its purpose is to retain the underlying layers. It is essential that each layer is placed in close approximation to the one before it, without air pockets. Each layer should also increase in size and degree of overlap from the wound to the outermost layer [1].

13. The use of antimicrobial agents in wound dressings

There is debate regarding the usefulness of topical antimicrobial agents for cutaneous wounds. It is believed that in the absence of infection, a topical antimicrobial is not necessary as well as the wound is taken care of well. However, there is evidence that infection prolongs wound healing. Therefore, there is the need to distinguish between bacterial colonization of the wound and true infection that actually compromises the tissue [1].

14. The use of silver and iodine to control wound infection

Many dressings incorporate compounds such as silver and iodine to control infection. Silver is an anion with strong antimicrobial activity. Therefore, it has been used for decades to treat wound infections. The mechanism by which silver ions kill microorganisms is by inhibiting bacterial-specific enzymes that are important in bacterial cell wall synthesis and gene transcription. There is evidence that silver-containing dressings considerably decrease the

incidence of burn wound –associated sepsis and bacteremia as well as shorten hospitalization time. Additionally, silver ions reduce the levels of matrix metalloproteinases that are upregulated in non-healing wounds [28].

15. Silver-containing dressings

At the original introduction of silver-containing dressings, silver ions were present in the form of silver nitrate and silver sulfadiazine. However, newer formulations are composed of high density polyethylene mesh that is impregnated with nanocrystalline silver. Acticoat, Actisorb Silver, Contreet Foam, Contreet Hydrocolloid and Silverlon and examples of nanocrystalline silver dressings [45].

These dressings offer antibiotic activity against both gram-positive and gram-negative bacteria. Each of these dressings is able to release antibacterial levels of silver for 3–7 days. Research has indicated that silver impregnated dressings can enhance the short-term healing of wounds and ulcers [1].

However, recent studies have shown, that in certain patient populations, the use of silver-containing dressings is contraindicated due to potential toxicity. These include, patients with surgical wounds that are at low risk for infection, pregnant or lactating women, patients who are sensitive or allergic to silver or metals, patients with wounds being treated with an enzymatic debridement agent, patients with wounds that have no signs and symptoms of infection present, chronic wounds that are healing as expected, patients with wounds in or near sites that are being treated or have been treated with radiotherapy, patients with wounds in which slough or necrotic tissue is present, as well as wounds that are colonized with multiple organisms or biofilms [46].

Additionally, there have been reports of silver toxicity in the setting of treating large-surface-area wounds with silver impregnated dressings. Therefore, silver toxicity should be considered when patients present with leukopenia [47].

16. Use of iodine in wound dressing

Iodine has been used to help with wound healing for over 150 years [48]. Povidone-iodine is a frequently used antiseptic which can actually inhibit wound healing [49]. However, there are newer dressings, such as cadexomer-iodine polymer that slowly release iodine from dextran beads. These do not appear to have toxic effects on keratinocytes. In this dressing, there is a low level of iodine that is slowly released from the beads.

Iodine wound dressings are recommended for exudative wounds, including leg ulcers and are not appropriate in the treatment of autoimmune bullous disease. Caution must be taken when using these dressings in patients with a history of thyroid disease. These dressings should be avoided in young children, pregnant or lactating women or patients with a known or suspected iodine insensitivity [49].

17. Recommended wound care in immunobullous disease

17.1. Treatment of pemphigus vulgaris, pemphigoid and Steven Johnson syndrome in a burn unit

Steven-Johnsons syndrome, toxic epidermal necrosis, pemphigus vulgaris and bullous pemphigoid display disruption of the skin layers or its blood supply and produce similar lesions that mimic a burn injury. When greater than 60% of total body surface area is involved, it is recommended that patients are admitted to a burn care unit. In the unit, these patients are provided with a proper environment, temperature, humidity and infrared lamps to prevent infection. High mortality and morbidity are reduced by proper handling and hospitalization in a burn care unit. Wound management in these diseases require similar care to burns, as well as fluid resuscitation and dietary care [50].

17.2. General nursing care pemphigus and pemphigoid

The best approach to the care of blistered skin has not yet been definitively established. There is currently controversy on how to deal with small tense blisters. While some resources recommend daily rupturing of tense blisters for reducing lateral extension of the blister edges, other resources advocate for leaving blisters intact, to prevent secondary infection. However, large blisters should be aspirated with a sterile needle, to keep the blister roof in place. Raw areas need to be cleaned by antiseptics or normal saline and then covered by a non-adhesive dressing. Excessive skin manipulation and trauma should be avoided in active pemphigus vulgaris [51]. When patients have oral mucosal lesions, it is recommended them to maintain a soft diet, use soft tooth brushes, antiseptic gargles and prophylaxis against oral candidiasis [52].

The wound care in treating pemphigus vulgaris and bullous pemphigoid depends on the severity of the disease, the location of the lesions, as well as the total body surface area (TBSA) covered with lesions. While there have been several case studies published with different recommendations regarding wound care, each is individualized to the unique needs of the specific patient, and there is not yet one specific standard of care [52].

When patients who have extensive raw areas are hospitalized, they must be isolated to reduce cross-infection. Secondary bacterial (MRSA, pseudomonas) or viral (HSV) infections can occur. The use of antimicrobials is effective. Additionally, it is important to routinely monitor blood pressure and blood glucose levels. Steroid related complications frequently occur shortly or within 1 year of the start of systemic treatment in bullous pemphigoid. These include infection, worsening of diabetes or blood pressure, and pressure sores. These complications must be monitored so that the immunosuppressant dose can be adjusted if needed [53]. After prolonged hospitalization, MRSA colonization can occur. Additionally, a five-day decontamination regime with 4% chlorhexidine body wash and nasal mupirocin ointment may be considered when lesions resolve [51].

Typically, hospitalized patients with bullous pemphigoid have multiple comorbidities, and often present with generalized involvement, a more severe disease, recurrent relapses, higher morbidity and mortality. This occurs especially in the first year. Patients typically have a worse prognosis when they are bed bound, anemic, hypoalbuminemic or have a malignancy [51].

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17.3. Severe disease

In severe disease, the premise of care is very similar to patients being treated for partial thickness burn therapy. Frequently in pemphigus vulgaris and bullous pemphigoid, the body is covered with intact bullae and partial-thickness wounds from head to toe. Serous sanguineous fluid drains onto the linens, which exacerbates pain since once it dries it becomes stuck and unstuck to bed sheets and bandages [54] (**Figure 7**).

In severe pemphigus and pemphigoid, various goals of wound care management have been identified. These include relieving severe pain, preventing infection and decreasing bioburden, enhancing regeneration of the dermis and the epidermis, protecting the periwound skin from maceration, encouraging patient mobility and quality of life, providing nutritional support for tissue repair, as well as treating the underlying cause of the wound [55].

All dressing products used for these patients must be nonadherent. Following chemotherapy for severe lymphocytic leukemia, a 66 year old female with pemphigus vulgaris was given a daily dressing which utilized a foaming skin care wash [56]. Additionally, there was a nonsting barrier to protect the intact skin and hydrogel sheets to provide a moist environment. An advanced ionized silver wound-care product in the form of a gel or powder was considered given the possibility of wound infection. Xerofoam gauze is an optimal product to add over the hydrogel sheet to prevent it from drying out and to stabilize it. At the start of the wound care, large abdominal dressings were also applied over the Xerofoam gauze to absorb the drainage. Above that, various kinds of stretch bandages or nets were placed to secure the

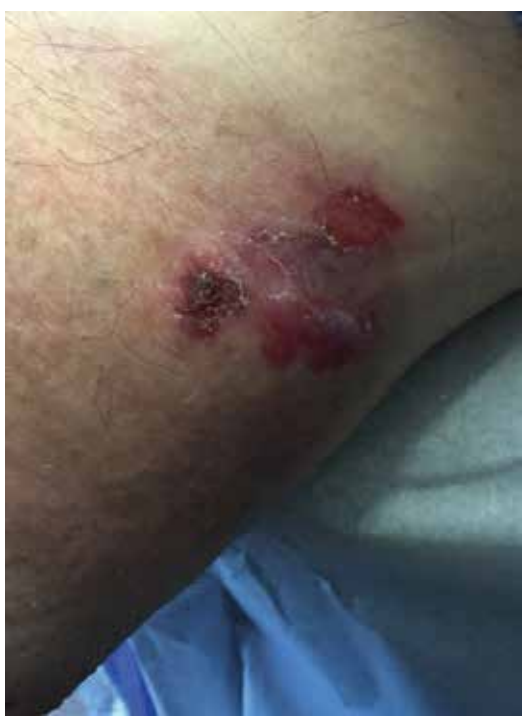

Figure 7. Pemphigus vulgaris lesions on patient's leg.

dressing [54]. It is important to keep the skin surface moist and not open to air for healing and pain management.

Ultimately, the wound care plan focuses on reducing pain, preventing infection by gentle cleansing and preventing scarring by providing a moist environment. Additionally, nutrition is a key aspect of care, due to the loss of protein and other essential components in the serous sanguineous drainage [51] (**Table 3**).

17.4. Silver containing hydrofiber dressings for pemphigus vulgaris wounds

Recent studies have advocated for the use of silver-containing hydrofiber dressings as effective adjunct in the treatment of pemphigus vulgaris. Following the application of these dressings,

1. Clean the wound
    - **a.** Use a foaming skin care wash (Cetaphil or Cerave)
        - i. allows cleaning of the wound without pain, it is nonabrasive
    - **a.** Apply directly to wounds and then gently rinse off
    - **b.** Shower
    - **c.** Wrap in a warm bath blanket to maintain temperature, which is conducive to wound healing
2. Protect the periwound skin
    - **a.** "No-sting" skin barrier similar to applying a thin film on the intact skin as a shield against excessive moisture
    - **a.** No-sting is painless because alcohol is not an ingredient
        - **i.** Spray (StingFree)
        - **ii.** Pad (StingFree)
3. Provide a moist environment
    - **a.** Hydrogel sheet
        - **i.** Gelled water formed into a flat dressing
        - **ii.** 4 × 4 or 6 × 8 inches
    - **b**. Cover wound with film with the sticky side placed on the wound bed
4. Optional step: placement of a fine mesh nonadherent gauze which is impregnated with petrolatum and 3% bismuth tribomophenate
    - **a**. the gauze secures the hydrogel and provides additional protection of the periwound skin
5. Optional step: If wound drainage is excessive, then heavy ABD pads (cotton dressing pads) can be applied to wick away the drainage
6. Secure dressing with Kerlix, a conforming, 100% woven gauze
7. A self-adhesive wrap with minimal stretch provides the finishing touch to the dressing, allowing the patient mobility and improved quality of life

Table 3. Wound care plan [55].

there was marked improvement in wound healing and decreased patient discomfort [45]. Additionally, topical measures such as hydrotherapy, topical glucocorticoids and topical antimicrobial agents also help to control the disease. Unfortunately, some patients are resistant to these conventional therapies. Previous studies have supported the use of silver containing hydrofiber dressing patches (SHD) for managing partial thickness burns and toxic epidermal necrolysis [45].

SHD is made from the hydrocolloid polymer carboxymethylcellulose to which silver ions are attached. The dressing fibers absorb wound exudate and swell to form a soft cohesive gel that covers the wound surface. It has the ability to absorb large volumes of exudate, up to 20 times its weight in fluid. Therefore, it is suitable for heavy exudating wounds. Since it retains fluid in the dressing over the wound, it dehydrates less quickly than other dressings and promotes a moist healing environment. Additionally, it limits lateral movement of fluid and avoids maceration of the surrounding skin [45].

A recent case of pemphigus vulgaris involving 62% of the total body surface area (TBSA), examined the effectiveness of SHD for wound healing [45]. Following the use of SHD, the patient showed dramatic wound healing with reduced patient discomfort. Specifically, after starting the SHD therapy, there was a marked improvement in wound healing and the affected TBSA decreased from 62–5% over just 4 weeks. After just 1 week after starting the SHD therapy, no new skin lesions were noted. Not only did this treatment appear to be effective in wound healing, but it is also less time consuming. Dressing changes only took 45 minutes every 3 days with SHD, compared with 2 hours every day with hydrotherapy and SSD care. It was also noted that the patient experienced less pain and discomfort during the dressing changes.

17.5. The use of nano-silver dressings (Acticoat) in pemphigus vulgaris

As stated above, over the past three decades, nanocrystalline silver dressings have provided antimicrobial, pro-healing, and anti-inflammatory activity. Antibacterial effects have minimized the frequency of wound dressing and have improved the healing of acute and chronic lesions from superficial to deep layers. Acticoat is a silver biologic dressing containing a 15 nm bactericidal coat of nanocrystallized ions of silver in a cluster structure. It coats many cells that are exposed to infection and protects them through continuous silver ion release. Acticoat is able to eliminate at least 150 types of microorganisms after 30 min of use. Nanocrystaline skin dressings have been found to be beneficial in many skin lesions, including burns. It has also been found that compared with traditional wound dressings such as silver sulfadiazine, nanocrystalline coated silver dressings not only have shortened hospital stays and less frequency of wound dressing changes, but there is also improved wound healing and balancing overall costs, in addition to a higher satisfaction rate by patients [57].

Masjedi et al. compared a nanocrystalline silver dressing with a regular sulfadiazine normal dressing (the control) in the treatment of pemphigus vulgaris lesions [58]. 16 patients each received both an experimental and control dressing on symmetrical lesions. Qualitative wound score (QWS) and clinical photography were conducted during treatment for 4 weeks. After 4 weeks, QWS decreased by 1.94 more in the experimental compared to baseline than in

the control group. Ultimately, after 4 weeks, QWS decreased by 1.95 more in the experimental compared to baseline than in the control group. Additionally, after 4 weeks, Acticoat showed complete healing in 13 cases in addition to one acceptable healing. It was also noted that Acticoat shortened hospital stay and provided easier handling. While this study showed that the nanocrystalline silver dressing, Acticoat was superior to the silver sulfadiazine dressing in treating vesicobullous lesions, there still has not been a trial which examined the effect of this dressing on wound healing time without superinfection and on costs and complications.

17.6. The use of banana leaf for wound management of patients with toxic epidermal necrolysis

Steven Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening allergic reactions usually to medications, which require immediate treatment. These two diseases can be differentiated by the surface area affected by epidermal necrosis. SJS only involves skin lesions on less than 10% of the total body surface area, whereas TEN involves 10–30% skin lesions with severe inflammation of mucosal tissues.

The main goal is to prevent infection and to encourage healing. Wound care for these diseases is similar to severe cases of pemphigus vulgaris and bullous pemphigoid.

Modern medical supplies for wound management include paraffin coated mesh, Vaseline, petroleum, disinfectant dressings with silver-compounds such as nanocrystalline silver dressing, silver hydrofiber, as well as silicone silver foam dressing. These dressings are all very expensive, and efforts must be made to find dressings, which reduce cost as well as pain level.

Recent studies have found that using aloe vera resulted in better healing rate than silver sulfadiazine (SSD) [59]. Additional studies have explored using honey dressing on burns and found that they resulted in better healing and lower rate of necrosis compared to SSD [60]. In a comparative study between boiled potato peel bandages and sterile banana leaf, there were similar healing rates between the two, but the banana leaf was more cost effective and did not cling to the wound as much [61].

Uppanisakorn et al. examined the use of a sterile banana leaf dressing, which allowed the patient to be discharged swiftly and reduced the cost of treatment by eight times. When supportive therapy using banana leaf dressing was given, the patient was able to be discharged within 12 days [62].

There is much promise in the use of sterile banana leaf dressings for wound management. The price is 160 times lower than the cost of paraffin gauze. It has also been known to decrease pain and increase ease and speed of wound healing. The only caution of using banana leaf dressings is the potential for infection from contamination.

Further research must be done to determine the efficacy of banana leaf dressings for patients with pemphigus and pemphigoid.

17.7. Pemphigoid wound care – specific considerations

Pemphigoid most frequently affects elderly adults. As a result, these patients are frequently dependent upon relatives or health care workers for personal care activities. Therefore, their

ability to comply with treatment must be considered. Topical corticosteroid therapy is not a favorable option for patients who are unable to properly apply the medication and lack access to assistance. In this patient population, a combination of comorbidities and adverse effects of treatment, rather than the direct effects of disease, are what actually lead to morbidity and mortality. Treatment should be conservative and a minimal amount of medication required to achieve remission should be given [50].

While a high potency topical corticosteroid is often used for patients with bullous pemphigoid, if the patients are unable to properly administer topical treatment, a systemic glucocorticoid will be required. These are typically more accessible to patients at a lower cost, and have increased compliance. In addition, often when patients have widespread involvement, systemic therapy is faster and easier to administer than topical therapy [63].

17.8. Mucosal wound care

Oral blisters in pemphigus vulgaris have a very thin roof and rupture as a result of oral traumas, which leads to multiple chronic painful bleeding ulcers and erosions that heal with difficulty (**Figure 8**). There are patient reports of pain in the oral cavity as well as a burning sensation that occurs when they consume spicy or acidic foods. While blisters can appear at any localization of the oral mucosa, they most frequently appear in sites that are subjected to friction, including the soft palate, buccal mucosa, ventral tongue, gingiva, and lower lip. Infrequently, there are lesions on the gingiva [64]. In more advanced stages of pemphigus vulgaris, desquamative or erosive gingivitis can be observed. There are other oral manifestations, including sialorrhea, halitosis and the continuous formation of brown or blackish crusts at the vermillion border. Pemphigus vulgaris can involve the conjunctiva, nasal, pharyngeal, laryngeal, esophageal, genital and anal mucosa as well. Blisters typically rupture more easily on the mucosa than on the skin [64].

Oral lesions present a challenge, give their slow response to treatment in comparison to cutaneous lesions. When patients have low titers of circulating antibodies, lesions can be

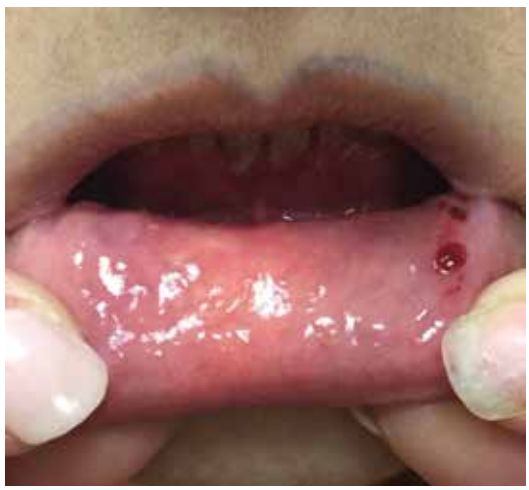

Figure 8. Patient with pemphigus vulgaris in the oral mucosa.

controlled temporarily with mouthwashes or topical creams that contain corticosteroids. These include 0.1% triamcinolone acetonide in orabase, 0.05% fluocinolone acetonide, 0.05% clobetasol propionate, or 0.05% halobetasol. Intralesional injection of triamcinolone acetonide (20 μg/L) or paramethasone every 5–15 days can be used in refractory lesions. However, the treatment should be withdrawn if symptoms do not improve after three injections [64].

To improve the wellbeing of patients suffering from mucosal lesions, it is recommended to administer analgesics, maintain oral hygiene using diluted antiseptic (chlorohexidine) mouthwashes, periodontal treatment, following a soft diet without irritants, checking prosthetic restorations, and applying anti-candida therapy in patients on long-term corticosteroid treatments [64].

Since oral trauma can trigger or worsen pemphigus vulgaris, Bystrn et al. recommended the prophylactic administration of 20 mg prednisone/day in addition to the patient's normal requirement for 5–7 days before any dental procedure that is associated with trauma to the gums [2].

The nostrils should be cleaned daily with a sterile cotton swab that is moistened with isotonic sterile sodium chloride solution. Antibiotic ointment should also be applied to the nostrils. The mouth should be rinsed a few times a day using a syringe with isotonic sterile sodium chloride solution [2].

18. Conclusion

There is current controversy on how to achieve optimal wound management of this disease. When the disease becomes severe, patients are typically admitted to the burn unit. Therefore, the supportive care resembles that performed for severe thermal burns TEN. It aims at minimizing potential complications which may ultimately lead to patient mortality. For instance, it aims to avoid hypovolemia, electrolyte imbalance, renal insufficiency and sepsis [24].

Careful wound care, hydration and nutritional support are critical and performed in an intensive care unit if there is epidermal detachment involving 10–20% or more of body surface area. Current wound care recommendations include using controlled pressure as well as thermoregulated bed and sheets. It is essential for all procedures to occur in a sterile environment and for venous catheters to only be placed in regions of non-involved skin [65].

It is advised that wound care be performed under the guidance of a dermatologist, due to the complex issues these patients face. Cutaneous care should include the face, eyes, nose, mouth, ear, anogenital region, axillary folds and interdigital spaces. When cutaneous areas are non-detached, the must be kept dry and not manipulated. However, detached cutaneous areas should be covered with Vaseline gauze until reepithelization has occurred [24].

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References

[1] Bolognia J, Schaffer JV, Duncan KO, Ko CJ. Dermatology Essentials. Oxford: Saunders/Elsevier; 2014

[2] Bystryn JC, Rudolph JL. Pemphigus. Lancet. 2005;**366**(9479):61-73. DOI: 10.1016/s0140-6736(05)66829-8

[3] Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. Journal of the American Academy of Dermatology. 2008;**58**(6):1043-1046. DOI: 10.1016/j.jaad.2008.01.012

[4] Hammers CM, Stanley JR. Mechanisms of disease: Pemphigus and bullous pemphigoid. Annual Review of Pathology. 2016;**11**:175-197. DOI: 10.1146/annurev-pathol-012615-044313

[5] Amagai M. Autoimmune and infectious skin diseases that target desmogleins. Proceedings of the Japan Academy. Series B, Physical and Biological Sciences. 2010;**86**(5):524-537. DOI: 10.2183/pjab.86.524

[6] Sitaru C, Mihai S, Zillikens D. The relevance of the IgG subclass of autoantibodies for blister induction in autoimmune bullous skin diseases. Archives of Dermatological Research. 2007;**299**(1):1-8. DOI: 10.1007/s00403-007-0734-0

[7] Xu H-H, Werth VP, Parisi E, Sollecito TP. Mucous membrane pemphigoid. Dental Clinics of North America. 2013;**57**(4):611-630. DOI: 10.1016/j.cden.2013.07.003

[8] Mehren CR, Gniadecki R. Epidermolysis bullosa acquisita: Current diagnosis and therapy. Dermatology Reports. 2011;**3**(3):e38. DOI: 10.4081/dr.2011.e38

[9] Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: Challenges and solutions. Clinical, Cosmetic and Investigational Dermatology. 2015;**8**:521-527. DOI: 10.2147/CCID.S75908

[10] Tamgadge S, Tamgadge A, Bhatt DM, Bhalerao S, Pereira T. Pemphigus vulgaris. Contemporary Clinical Dentistry. 2011;**2**(2):134-137. DOI: 10.4103/0976-237X.83074

[11] Pires CAA, Viana VB, Araújo FC, Müller SFR, de Oliveira MS, Carneiro FRO. Evaluation of cases of pemphigus vulgaris and pemphigus foliaceus from a reference service in Pará state, Brazil. Anais Brasileiros de Dermatologia. 2014;**89**(4):556-561. DOI: 10.1590/abd1806-4841.20142679

[12] Schmidt E, Zillikens D. The diagnosis and treatment of autoimmune blistering skin diseases. Deutsches Ärzteblatt International. 2011;**108**(23):399-405. DOI: 10.3238/arztebl.2011.0405

[13] Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. Therapeutics and Clinical Risk Management. 2008;**4**(3):617-626

[14] Murrell DF, Daniel BS, Joly P, Borradori L, Amagai M, Hashimoto T, et al. Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. Journal of the American Academy of Dermatology. 2012;**66**(3):479-485. DOI: 10.1016/j.jaad.2011.06.032

[15] Zheng Z, Nguyen C, Zhang X, Khorasani H, Wang JZ, Zara JN, et al. Delayed wound closure in fibromodulin-deficient mice is associated with increased TGF-β3 signaling. The Journal of Investigative Dermatology. 2011;**131**(3):769-778. DOI: 10.1038/jid.2010.381

[16] Anderson K, Hamm RL. Factors that impair wound healing. The Journal of the American College of Clinical Wound Specialists. 2012;**4**(4):84-91. DOI: 10.1016/j.jccw.2014.03.001

[17] Song F, Li B, Stocum DL. Amphibians as research models for regenerative medicine. Organogenesis. 2010;**6**(3):141-150

[18] Stewart S, Stankunas K. Limited dedifferentiation provides replacement tissue during Zebrafish fin regeneration. Developmental Biology. 2012;**365**(2):339-349. DOI: 10.1016/j.ydbio.2012.02.031

[19] Hasegawa T, Hall CJ, Crosier PS, Abe G, Kawakami K, Kudo A, Kawakami A. Transient inflammatory response mediated by interleukin-1β is required for proper regeneration in zebrafish fin fold. eLife. 2017;**6**:e22716. DOI: 10.7554/eLife.22716

[20] Yates CC, Hebda P, Wells A. Skin wound healing and scarring: Fetal wounds and regenerative restitution. Birth Defects Research. Part C, Embryo Today : Reviews. 2012;**96**(4):325-333. DOI: 10.1002/bdrc.21024

[21] Larson BJ, Longaker MT, Lorenz HP. Scarless fetal wound healing: A basic science review. Plastic and Reconstructive Surgery. 2010;**126**(4):1172-1180. DOI: 10.1097/PRS.0b013e3181eae781

[22] Torricelli AAM, Singh V, Santhiago MR, Wilson SE. The corneal epithelial basement membrane: Structure, function, and disease. Investigative Ophthalmology & Visual Science. 2013;**54**(9):6390-6400. DOI: 10.1167/iovs.13-12547

[23] Saparov A, Chen C-W, Beckman SA, Wang Y, Huard J. The role of antioxidation and immunomodulation in postnatal multipotent stem cell-mediated cardiac repair. International Journal of Molecular Sciences. 2013;**14**(8):16258-16279. DOI: 10.3390/ijms140816258

[24] Donners MMPC, Bai L, Lutgens SPM, Wijnands E, Johnson J, Schurgers LJ, et al. Cathepsin K deficiency prevents the aggravated vascular Remodeling response to flow cessation in ApoE(−/−) mice. PLoS One. 2016;**11**(9):e0162595. DOI: 10.1371/journal.pone.0162595

[25] Chadwick SL, Yip C, Ferguson MWJ, Shah M. Repigmentation of cutaneous scars depends on original wound type. Journal of Anatomy. 2013;**223**(1):74-82. DOI: 10.1111/joa.12052

[26] Rittié L. Cellular mechanisms of skin repair in humans and other mammals. Journal of Cell Communication and Signaling. 2016;**10**(2):103-120. DOI: 10.1007/s12079-016-0330-1

[27] Grim SA, Slover CM, Sankary H, Oberholzer J, Benedetti E, Clark NM. Risk factors for wound healing complications in sirolimus-treated renal transplant recipients. Transplantation Proceedings. 2006;**38**(10):3520-3523. DOI: 10.1016/j.transproceed.2006.10.065

[28] Yang JY, Huang CY, Chuang SS, Chen CC. A clinical experience of treating exfoliative wounds using nanocrystalline silver-containing dressings (Acticoat). Burns. 2007;**33**(6):793-797. DOI: 10.1016/j.burns.2006.11.010

[29] Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A, et al. Epithelialization in wound healing: A comprehensive review. Advances in Wound Care. 2014;**3**(7):445-464. DOI: 10.1089/wound.2013.0473

[30] Hunt TK, Dunphy JE. Fundamentals of Wound Management. New York: Appleton Century Crofts; 1979

[31] Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature. 1962;**193**:293-294

[32] Gannon HS, Donehower LA, Lyle S, Jones SN. Mdm2-p53 signaling regulates epidermal stem cell senescence and premature aging phenotypes in mouse skin. Developmental Biology. 2011;**353**(1):1-9. DOI: 10.1016/j.ydbio.2011.02.007

[33] Bootun R. Effects of immunosuppressive therapy on wound healing. International Wound Journal. 2013;**10**(1):98-104. DOI: 10.1111/j.1742-481X.2012.00950.x

[34] Burgos FJ, et al. Post-kidney transplant surgical complications under new immunosuppressive regimens. Transplantation Proceedings. 2006;**38**(8):2445-2447

[35] Valente JF, et al. Comparison of sirolimus vs. mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. American Journal of Transplantation. 2003;**3**(9):1128-1134

[36] Selman SM, et al. Rituximab delays wound healing and decreases white blood cell count in male mice. 2017;**2017**:5

[37] Fauci AS. Corticosteroids in autoimmune disease. Hospital Practice (Office Ed.). 1983; **18**(10):99-103, 107-118, 113-104

[38] Guo S, DiPietro LA. Factors affecting wound healing. Journal of Dental Research. 2010;**89**(3):219-229. DOI: 10.1177/0022034509359125

[39] Eaglstein WH, Davis SC, Mehle AL, Mertz PM. Optimal use of an occlusive dressing to enhance healing. Effect of delayed application and early removal on wound healing. Archives of Dermatology. 1988;**124**(3):392-395

[40] Kaigler D, Avila G, Wisner-Lynch L, Nevins ML, Nevins M, Rasperini G, et al. Platelet-derived growth factor applications in periodontal and peri-implant bone regeneration. Expert Opinion on Biological Therapy. 2011;**11**(3):375-385. DOI: 10.1517/14712598.2011.554814

[41] Wankell M, Munz B, Hübner G, Hans W, Wolf E, Goppelt A, Werner S. Impaired wound healing in transgenic mice overexpressing the activin antagonist follistatin in the epidermis. The EMBO Journal. 2001;**20**(19):5361-5372. DOI: 10.1093/emboj/20.19.5361

[42] Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiological Reviews. 2003;**83**(3):835-870. DOI: 10.1152/physrev.00031.2002

[43] Li W, Dasgeb B, Phillips T, Li Y, Chen M, Garner W, Woodley DT. Wound-healing perspectives. Dermatologic Clinics. 2005;**23**(2):181-192. DOI: 10.1016/j.det.2004.09.004

[44] Sood A, Granick MS, Tomaselli NL. Wound dressings and comparative effectiveness data. Advances in Wound Care. 2014;**3**(8):511-529. DOI: 10.1089/wound.2012.0401

[45] Wu CS, Hsu HY, Hu SC, Chiu HH, Chen GS. Silver-containing hydrofiber dressing is an effective adjunct in the treatment of pemphigus vulgaris. The Kaohsiung Journal of Medical Sciences. 2009;**25**(11):622-627. DOI: 10.1016/S1607-551X(09)70567-4

[46] Leaper D. Appropriate use of silver dressings in wounds: International consensus document. International Wound Journal. 2012;**9**(5):461-464. DOI: 10.1111/j.1742-481X.2012.01091.x

[47] LaRiviere CA, Goldin AB, Avansino J. Silver toxicity with the use of silver-impregnated dressing and wound vacuum-assisted closure in an immunocompromised patient. The Journal of the American College of Certified Wound Specialists. 2011;**3**(1):8-12. DOI: 10.1016/j.jcws.2011.05.002

[48] Cooper RA. Iodine revisited. International Wound Journal. 2007;**4**(2):124-137. DOI: 10.1111/j.1742-481X.2007.00314.x

[49] Goldenheim PD. An appraisal of povidone-iodine and wound healing. Postgraduate Medical Journal. 1993;**69**(Suppl 3):S97-105

[50] Castana O, Makrodimou M, Michelakis D, Tsandoulas Z, Alexakis D. Diseases mimicking a burn - outcome and treatment. Annals of Burns and Fire Disasters. 2005;**18**(3):130-132

[51] Brandão EDS, dos Santos I, Lanzillotti RS, Ferreira AM, Gamba MA, Azulay-Abulafia L. Nursing diagnoses in patients with immune-bullous dermatosis. Revista Latino-Americana de Enfermagem. 2016;**24**:e2766. DOI: 10.1590/1518-8345.0424.2766

[52] Fishman TD. Wound assessment and evaluation…Bullous pemphigoid. Dermatology Nursing. 1999;**11**(6):436-437

[53] McCuin JB, Hanlon T, Mutasim DF. Autoimmune bullous diseases: Diagnosis and management. Dermatology Nursing. 2006;**18**(1):20-25

[54] Miletta N, Miller ME, Lam T, Chung KK, Hivnor C. The management of pemphigus vulgaris in a burn intensive care unit: A case report and treatment review. Journal of Burn Care & Research. 2014;**35**(5):e357-e363. DOI: 10.1097/bcr.0000000000000049

[55] Blackett AV. Managing Painful Surface Wounds. Oncology(Oncology Nursing, Palliative and Supportive Care); 2007

[56] Hayanga AJ, Lee TM, Pannucci CJ, Knipp BS, Olsen SH, Wang SC, Napolitano LM. Paraneoplastic pemphigus in a burn intensive care unit: Case report and review of the literature. Journal of Burn Care & Research. 2010;**31**(5):826-829. DOI: 10.1097/BCR.0b013e3181eed4b4

[57] Masjedi H. The healing effects of nano-silver dressings in pemphigus vulgaris. Wounds Middle East. 2015;**2**(3):33-37

[58] Masjedi H. In: Malekzad F, editor. The Healing Effect of Nano-Silver Dressings in Pemphigus Vulgaris. Vol. 2. Tehran, Iran: Wounds Middle East; 2015. p. 6

[59] Khorasani G, Hosseinimehr SJ, Azadbakht M, Zamani A, Mahdavi MR. Aloe versus silver sulfadiazine creams for second-degree burns: A randomized controlled study. Surgery Today. 2009;**39**(7):587-591. DOI: 10.1007/s00595-008-3944-y

[60] Baghel PS, Shukla S, Mathur RK, Randa R. A comparative study to evaluate the effect of honey dressing and silver sulfadiazene dressing on wound healing in burn patients. Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India. 2009;**42**(2):176-181. DOI: 10.4103/0970-0358.59276

[61] Jurjus A, Atiyeh BS, Abdallah IM, Jurjus RA, Hayek SN, Jaoude MA, et al. Pharmacological modulation of wound healing in experimental burns. Burns. 2007;**33**(7):892-907. DOI: 10.1016/j.burns.2006.10.406

[62] Uppanisakorn S, Boonyarat J. Wound management of patients with toxic epidermal necrolysis using banana leaf: A case study. Advanced Practices in Nursing. 2017;**02**

[63] Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. British Journal of Dermatology. 2012;**167**(6):1200-1214. DOI: 10.1111/bjd.12072

[64] Arpita R, Monica A, Venkatesh N, Atul S, Varun M. Oral pemphigus vulgaris: Case report. Ethiopian Journal of Health Sciences. 2015;**25**(4):367-372

[65] Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. Annals of Allergy, Asthma & Immunology. 2006;**97**(3):272-280; quiz 281-273, 320. DOI: 10.1016/s1081-1206(10)60789-2

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Autoimmune bullous diseases are a group of rare skin diseases characterized by intraepidermal and subepidermal bullae formations due to autoantibodies directed against the structural proteins of the epidermis or the dermal-epidermal junction. Early and correct diagnosis and adequate treatment of autoimmune bullous diseases are important as they cause morbidity and mortality in the affected patients. This book, which gives detailed information about autoimmune bullous diseases, has two sections and nine chapters with sixteen contributing authors. The first section describes the structure and tasks of desmosomes and basement membrane zone, which consist of the major antigens of skin integrity targeted by autoantibodies. The second section is about the epidemiology, etiopathogenesis, mucocutaneous, histopathologic and laboratory findings, and therapy of autoimmune bullous diseases.

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