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Updates on Laryngology

Edited by Balwant Singh Gendeh

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Contributors
Tarang Patel, Garima Anandani, María Elena Buenrostro Espinosa, Samantha Rivero Borrell, Jorge Francisco Piña Rubio, Maria Fernanda Ochoa Cortez, Lesle Hernandez Uvence, Liz Marlene Montes Sandoval, Shaili Priyamvada, Rasmika Kanakarajan, Kanakarajan N.K, Sapna S. Nambiar, Slimcy Shylen, Suma Radhakrishnan, Giuseppe Leoncini, Vaishali Waindeskar, Anuj Jain, Ashutosh Kaushal, Pooja Thaware, Garima Chamania, Syahrial M. Hutauruk, Khoirul Anam, Elvie Zulka Kautzia Rachmawati, Balwant Singh Gendeh, Hardip Singh Gendeh

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Meet the editor

Dr. Balwant Singh Gendeh is a senior consultant ENT surgeon with a sub-specialty interest in rhinology (allergy, sinonasal diseases, endoscopic sinus, anterior and ventral skull base surgery, and functional and cosmetic nasal surgery). He has been a resident ENT Consultant at Pantai Hospital Kuala Lumpur since 2014. Previously, he was an ENT registrar at the Royal Infirmary, Middlesbrough, United Kingdom (1993) and a J. William Fulbright Scholar at the University of Pittsburgh, USA (1997) at the Hospital of University of Pennsylvania (HUP), Philadelphia, USA, and St Joseph's Hospital, Chicago, USA. He received a diploma from the Fellowship Academy of Medicine Malaysia (FAMM) in 2000. His experience includes being a board chairman of the Malaysian American Commission on Educational Exchange (MACEE), an international fellow of the American Academy of Otolaryngology, Head and Neck Surgery, and a fellow of the Academy of Sciences Malaysia (FASc). Dr. Gendeh has written ninety-eight scientific papers and thirty-eight book chapters and edited nine books.

Contents

Preface

This book discusses selected topics on the larynx and related problems, providing insight into advancements in the field. It is organized into five sections on "Laryngeal Neuroregulation", "Laryngeal Examination", "Reflux-Associated Problems", "Laryngeal Airway and Lesions", and "Laryngeal Airway Surgery" and includes the following nine chapters:

- Chapter 1: "Autonomic Neuroregulation in the Larynx and Its Clinical Implication"
- Chapter 2: "Laryngeal Examination with Laryngeal Mirror and Laryngoscopy"
- Chapter 3: "Updates on Laryngo-Pharyngeal Reflux (LPR) and Its Management"
- Chapter 4: "Vocal Cord Paralysis"
- Chapter 5: "Laryngeal Leukoplakia: A Focus on Histology"
- Chapter 6: "Laryngomalacia"
- Chapter 7: "Approach to the Difficult Airway in Laryngeal Cancer"
- Chapter 8: "Adenoid Cystic Carcinoma of Larynx"
- Chapter 9: "Challenges in Tracheostomy"

The chapters present new clinical and research developments as well as future perspectives on the many types of airway-related problems and lesions. It is a useful resource for ENT surgeons, laryngologists, head and neck surgeons, rhinologists, physicians, postgraduates, researchers, trainees and general practitioners with a special interest in larynx and related problems.

I would like to thank and congratulate the chapter authors for their excellent contributions and the time taken in writing the chapters and providing continued research, high-quality clinical observations, patient care, selfless teaching, and writing to advance knowledge in this field.

I would like to also thank the valuable teachers from whom I have gained knowledge throughout the years. I am grateful to IntechOpen for the final book project and print and for appointing me as the editor. My sincere thanks go to Author Service Manager Sara Tikel at IntechOpen for guiding me through the publication process and moving the book ahead in a timely fashion and to the technical editors for arranging the book in a uniform format.

I would like to dedicate this book to my spouse, children, and loved ones for all their patience and understanding.

Balwant Singh Gendeh, MBBS, MS(ORL-HNS), UKM, AM(Mal), FAMM, FASc (M'sia), FMSA
Retired Professor,
Department of Otorhinolaryngology, Head and Neck Surgery,
Universiti Kebangsaan Malaysia Medical Center,
Bangi, Malaysia

Senior Consultant,
ENT Resident Surgeon,
Rhinology, Allergy, Endoscopic Sinus and Skull Base Surgery,
Functional and Cosmetic Nasal Surgery,
Pantai Hospital,
Kuala Lumpur, Malaysia

Section 1

Laryngeal Neuroregulation

Chapter 1

Autonomic Neuroregulation in the Larynx and Its Clinical Implication

Syahrial M. Hutauruk, Elvie Zulka Kautzia Rachmawati and Khoirul Anam

Abstract

The central nervous system controls autonomic function through interconnected areas distributed throughout the neural axis known as central autonomic network (CAN). Central nervous systems are organized and control functions of the body and secretion of brain neurotransmitter. The autonomic nervous system includes all regions controlling autonomic, unconscious, and involuntary functions in body homeostasis. Vagal nerve is the longest and most complex nerve of the autonomic nervous system and plays a role in regulating innervation in the larynx. Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for clinical entities related to laryngology diseases, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and vocal cord dysfunction (VCD). This chapter reviews the pathogenesis and clinical findings of laryngeal disease related to autonomic nerve dysfunction.

Keywords: autonomic nerve dysfunction, vagal nerve, laryngopharyngeal reflux, sleep-disordered breathing, chronic cough, vocal cord dysfunction

1. Introduction

The central nervous system controls autonomic function in several areas. These areas are interconnected and then distributed throughout the neuroaxis. The area is called the central autonomous network (CAN); they control many other functions, of which the tasks of arousal and respiration are included [1]. One of the main outputs of this integrated network is mediated by preganglionic sympathetic and parasympathetic nerves. Hierarchically, the central autonomous control area has been arranged. The delivery of interoceptive information to the forebrain and the mediation of the cardiovascular, respiratory, gastrointestinal, and micturition reflex systems are regulated by the medullary and lower pons areas. The solitary tract nucleus (NTS), the reticular formation of the rostral ventrolateral medulla (VLM), rostral ventromedial medulla (RVMM), including the caudal raphe nucleus, medullary respiratory group, parabrachial nucleus (PB), and pelvic organ stimulation center (Barrington Nucleus) belong to this area [1, 2].

Autonomic control by modulating pain, response to stress, behavioral stimuli, and motor responses is integrated by areas in the upper pons and midbrain. These areas include the periaqueductal gray (PAG), the pedunculopontine tegmental nucleus/ pedunculopontine nucleus (PPT/PPN), and the locus coeruleus (LC) [3]. The hypothalamus takes over the generators of integrated autonomic, endocrine, and behavioral response patterns. This is done to ensure homeostasis and adaptation of the body to the environment. Hypothalamic autonomic output mainly comes from the paraventricular nucleus (PVH), dorsomedial nucleus (DMH), and lateral hypothalamic regions, including the orexin-synthesizing group of neurons (Orx, also known as hypocretin, Hcrt). The midcingulate cortex, anterior insular cortex, and amygdala are core areas of the telencephalon that control autonomic functions. Although the functional anatomy of the central control of autonomic function has been best characterized in experimental animals, several functional neuroimaging studies show that many of the same areas are activated during autonomic responses in humans [3, 4].

Autonomic functions are controlled by areas of the brain whose input is received and integrated from four main sources: interoceptive, humoral, limbic, and circadian. Spinal afferents relay information about interoceptive input from visceral, pain, and thermal receptors via ascending projections to lamina I of the dorsal horn or via cranial nerve afferents relayed in the NTS. The central autonomic regions, directly or indirectly, are reached by humoral signals from blood (such as glucose or cytokine levels) or cerebrospinal fluid (CSF, such as pH) via the circumventricular sensory organs. It is also the main neurotransmitter (sometimes along with the inhibitory amino acid glycine) of the circuits that control respiration and the sleep-wake cycle [5]. Autonomic, respiratory, and arousal circuits are modulated in state-dependent function by cholinergic, monoaminergic, and peptidergic influences from the brainstem, basal forebrain, hypothalamus, and local interactions mediated by local interactions by nitric oxide (NO), purines, endocannabinoids, and other signals [5, 6].

Sympathetic neurons and parasympathetic preganglionic neurons are the final effectors of the control center for autonomic function and are cholinergic. These neurons stimulate the excitatory signal of autonomic ganglia and enteric neurons through ganglion-type nicotinic receptors. Sympathetic preganglionic neurons are in the thoracolumbar spinal cord in segments T1 to L2, primarily in lamina VII, which forms the intermediolateral column (IML) and forms separate functional units that are selectively activated in response to different stimuli [5]. Sympathetic output is critical for maintaining blood pressure, local regulation of blood flow, thermoregulation, and response to exercise and internal or external stressors [5, 6]. Preganglionic sympathetic axons terminate in the paravertebral, prevertebral, terminal ganglia, and the adrenal medulla [6]. Norepinephrine is the main neurotransmitter in postganglionic sympathetic neurons. Except for the postganglionic sympathetic nerves, which innervate the sweat glands, they are cholinergic nerves and vasodilators in muscles and coronary arteries. From a functional point of view, the parasympathetic output can be further subdivided into outputs to cranial effectors via cranial nerves III, VII, and IX, output to the thoracic and abdominal viscera mediated by the vagus nerve (cranial nerve X), and outputs from the pelvic organs (bladder, rectum, and sexual organs) from sacral preganglionic neurons [4, 6]. Organ-specific reflexes are mediated by sympathetic output. Acetylcholine is the main neurotransmitter of the most parasympathetic ganglion and enteric nervous system (ENS) neurons. Noncholinergic neurons also mediate parasympathetic output, releasing NO and vasoactive intestinal polypeptide (VIP) [6].

2. Autonomic innervation in the larynx

Two conventionally divided subtypes of the autonomic nervous system (ANS), the sympathetic and parasympathetic nervous systems, are defined as peripheral efferent fibers. Recent studies have revealed the presence of general visceral afferent fibers. The autonomic innervation of the larynx had been veiled; however, recent studies have identified the autonomic nerve fibers in the larynx and illuminated the distribution of autonomic innervation [5, 6].

The postganglionic neurons of the laryngeal sympathetic nervous system have their cell body mainly in the superior cervical ganglion. The preganglionic neurons originate in the gray matter of the upper thoracic spinal cord. Sympathetic innervation of the larynx had been considered to be innervated along with superior or inferior laryngeal arteries and veins [6]. However, study by Hisa *et al.* [7] using the Falck-Hillarp method revealed that sympathetic innervation of the canine larynx is distributed via the superior laryngeal nerve and inferior laryngeal nerve. Hisa *et al.* [7] also revealed the detailed distribution of sympathetic nerve fibers in the laryngeal arteries and glands in the supraglottic, glottis, and subglottic using the Falck-Hillarp method and tyrosine hydroxylase (TH) immunohistochemistry. Tanaka *et al.* [8] describe that TH-immunoreactive nerve fibers were located in the vicinity of the basal lamina, but they never terminated or penetrated the basal lamina. Recent studies also revealed that there is a specific distribution of adrenergic neurons and noradrenergic nerve fibers in the larynx. Adrenergic fibers with fluorescent varicosities were observed around the base of the acini, blood vessels around intrinsic laryngeal muscles, gland cells, and myoepithelial cells in the submucosal gland region [8].

Many noradrenergic nerve fibers are contained in the superior laryngeal nerve and the recurrent laryngeal nerve. The supraglottic and subglottic submucosal glands received the noradrenergic nerve fibers from the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerve, respectively [7]. The external branch of superior laryngeal nerve supplies noradrenergic fibers to the cricothyroid muscle, while other intrinsic muscles received noradrenergic fibers from the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerve. The noradrenergic nerve fibers in the superior laryngeal nerve originated from the superior cervical ganglion. Noradrenergic nerve fibers are contained in the recurrent laryngeal nerve. Noradrenergic nerve fibers originate from the middle cervical ganglion and superior cervical ganglion via the vagus nerve [7, 9].

The parasympathetic nervous system plays a major role in the motor control of mucus secretion in the larynx. The cell body of the postganglionic neuron is present in the intralaryngeal ganglion [9]. As Yoshida *et al.* [10] describe, intralaryngeal ganglionic neurons have cholinergic nature and innervate vessels and glands. The cell body of the preganglionic neuron is in the dorsal nucleus of the vagal nerve. It projects the nerve fiber to the larynx via the vagal nerve and superior or inferior laryngeal nerve. ACh is the transmitter of motor neurons, pre- and postganglionic nerve fibers of parasympathetic nerves, and some of the sympathetic nerves [9, 10].

3. Heart rate variability analysis and autonomic nerve dysfunction

Heart rate (HR) is controlled by the autonomic nervous system. Changes in sympathetic and parasympathetic nervous system activity result in beat-by-beat variations in heart rate; therefore, these variations reflect autonomic nervous system

activity. Heart rate variability (HRV) is pathological, like ischemic heart disease, and decreased variability predicts poorer outcomes. Heart rate variability (HRV) is the result of the interaction between the autonomic nervous system (ANS) and sinoatrial node (SAN) activity; experts then assume that HRV is a surrogate marker for autonomic nerve dysfunction [11]. Heart rate variability (HRV) is the fluctuation in the time interval between adjacent heartbeats. HRV is thought to reflect the heart's ability to adapt to changing circumstances by detecting and rapidly responding to unpredictable stimuli. HRV measures neurocardiac function produced by heart-brain interactions and a dynamic nonlinear autonomic nervous system activity. HRV is an emergent response from interconnected regulatory systems working at various time scales that aids individuals in adapting to environmental and psychological stresses. Autonomic balance, blood pressure, gas exchange, intestinal motility, heart, rhythm, and vascular tone are all regulated by HRV (which refers to the diameter of blood vessels that regulate blood pressure) [11–13].

A healthy heart is not a metronome. Healthy heart oscillations are complex and nonlinear. The nonlinear system variability provides the flexibility to quickly adapt to an uncertain and changing environment. Optimal HRV status is always associated with health and self-regulation capacity, as well as adaptability or resilience of an individual. Higher levels of HRV, mediated by the vagal nerve at rest, were strongly associated with the performance of executive functions such as attention and emotional processing by the prefrontal cortex. The processing of afferent information by the intrinsic cardiac nervous system can modulate frontocortical activity and influence human executive and cognitive functions at higher levels [11].

HRV analysis is one of the modalities that can be used to assess overall cardiac health, especially with regard to the state of the autonomic nervous system, which is responsible for regulating heart activity and rhythm. HRV refers to the variation of the pulse interval or is related to the response to instantaneous changes in heart rate. Normal variability in heart rate is modulated by the autonomic nervous regulation of the heart and circulatory system. The balance mechanism of the sympathetic nervous system and the parasympathetic nervous system branch of the autonomic nervous system then control the heart rate. Increased sympathetic or reduced parasympathetic activity will cause accelerated cardiac activity; conversely, low sympathetic activity or high parasympathetic activity can cause cardiac deceleration. The degree of variability in heart rate can provide information about the function of neural control of heart rate and the ability of the heart to respond to changing conditions [11–13].

The classic measurement of HRV can be calculated from the electrocardiogram (ECG) i.e., at R-R intervals and consensus guidelines regarding appropriate indicators are available. Arroyo-Carmona *et al.* [12] used the R-R time series on several ECG studies to determine HRV. An ECG is a recording of the electrical activity in heart tissue, each of which is represented by different waves of different amplitude and duration. The morphology of the ECG is the result of the activities of the autonomic nerve system (ANS) and SAN and can be classified into two groups: positive deflection and negative deflection. This classic R-R measurement has been abandoned, considering that if it is analyzed in detail, the R-R distance will most likely indeed be a difference. Experts think that it can be influenced by the physiological regulation of baroreceptors and mechanosensory receptors in the cardiovascular system. Recent studies reveal that SAN also has its own variability; it is very important to separately evaluate the correlation of the two oscillators to use HRV to be a better surrogate marker for disease evaluation and even to describe physiological conditions such as aging and behavior [11, 14].

HRV can be measured by pulse photoplethysmography (PPG) method with finger plethysmogram (FPG). Measurement only takes about 20 minutes. The research of Lu *et al.* [11] has proven that although the PPG method has a quick process, it has been shown to produce results similar to Holter ECG measurements. Lu *et al.* [11] found a very strong correlation value ($r = 0.99$) and significant ($p < 0.000$) between PPG examination and Holter's ECG in both the frequency and time domains through linear regression analysis. Standard deviation normal to normal (SDNN) parameters and the low frequency/high frequency (LF/HF) ratio have also been shown to have fairly good sensitivity and specificity values (>82%) in detecting vagal autonomic disorders [11]. This HRV measurement method generally has three examination domains: frequency domain, time domain, and measurement aspects. The time-domain index on HRV will calculate the amount of variability in the interbeat interval (IBI) measurement, which is the period of time between successive heartbeats. The frequency-domain index divides the absolute or relative power distribution into four frequencies. Heart rate (HR) oscillations are classified as ultralow frequency (ULF), very low frequency (VLF), low frequency (LF), and high frequency (HF) by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [11–14].

4. Autonomic neuroregulation and its clinical implication in laryngology

Vagal nerve is the longest nerve of the autonomic nervous system and is one of the most important nerves in the body. Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for several clinical entities related to laryngology diseases, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and vocal cord dysfunction (VCD) [15].

Esophageal sphincter and gastrointestinal tract are innervated by the vagal nerve; therefore, deteriorated vagal nerve function may be an important factor in LPR regarding the incompetence of esophageal sphincter. Chronic inflammation in the larynx is also thought to be responsible in the occurrence of vagal neuropathy, a condition where laryngeal mucosa is in the hyposensitive and hypersensitive state simultaneously. This mechanism is thought to contribute in the pathogenesis of CC and VCD. Since CAN also plays an important role in regulating sleep-wake cycle, it is known that hypoxia and apnea during sleep will alter the neural modulation in the CAN through some neurotransmitters. These theories have supported the evidence on where autonomic nerve dysfunction could contribute in several laryngology diseases and SDB [1, 9, 15].

4.1 Laryngopharyngeal reflux (LPR)

LPR is an inflammatory condition of the upper gastrointestinal tract associated with the direct and indirect effects of the retrograde flow of gastroduodenal contents, which can cause morphological changes in the upper aerodigestive tract. LPR causes many laryngeal diseases. Reflux laryngitis, subglottic stenosis, granulomas, laryngeal carcinoma, contact ulcers, and vocal cord nodules are caused by LPR. Because the signs and symptoms of LPR are nonspecific and may be manifestations of other etiologies, e.g., infection, voice abuse, allergies, smoking, inhalation of irritants, alcoholism, and nonpathological changes, patients with LPR may experience prolonged and generalized suffering if their physician is unable to make a diagnosis [16, 17].

Coughing, hoarseness, and globus pharyngeus (a lump sensation in the throat) are the most prevalent symptoms. Hoarseness is a symptom that usually starts in the morning and improves over the day. Belafsky *et al.* [18] created the reflux symptom index (RSI), a nine-item questionnaire that can be completed in less than 1 minute for symptom assessment in patients with reflux illness. One of the challenges in diagnosing LPR is that the symptoms of the disease are less specific to confirm LPR, and thus, it is necessary to exclude other causative agents. In fact, there are still several studies showing an unrelated correlation between LPR symptoms, laryngeal findings, and findings from hypopharyngeal pH monitoring [18].

Belafsky *et al.* [19] developed the RFS, which includes an eight-item reflux clinical severity scale based on laryngoscopy findings. Subglottic edema, ventricular obliteration, erythema/hyperemia, vocal cord edema, widespread laryngeal edema, posterior commissure hypertrophy, granulomas, and thick endolaryngeal edema were all evaluated and graded on a scale of 0–4. According to Belafsky *et al.*, a practitioner can be 95% certain that a patient has LPR. The common findings of LPR are posterior commissure hypertrophy, subglottic edema, inflammation of the larynx or arytenoids, and the presence of thick endolaryngeal mucus [19].

LPR and gastroesophageal reflux disease (GERD) are considered as a continuum of similar basic pathophysiological mechanisms with some overlapping symptoms. The long-standing controversial differences between the two diseases still exist today. Most patients with throat complaints related to LPR deny the classic symptoms of GERD, especially heartburn. On the other hand, many LPR patients report no endoscopic findings of esophagitis, and the severity of esophagitis based on endoscopic examination is not related to the level of symptoms and signs of LPR. LPR and GERD are disease entities that are both caused by the retrograde flow of gastric contents, but the pathogenesis of these two conditions is different even though they are interrelated. The lower esophageal sphincter (LES) and gastrointestinal tract are innervated by the vagal nerve, and the pathogenesis of GERD itself mainly involves the presence of lesions in LES. According to research, the vagal nerve regulates the parasympathetic regulation of the gastrointestinal system. The malfunction of the LES and the transiently increased relaxation of the lower esophageal sphincter seen in GERD, which results in an increased amount of gastric acid going back into the esophagus, appear to be caused by decreased vagal nerve activity induced by inadequate autonomic regulation [18, 20, 21].

It is also known that there is a relationship between gastrointestinal symptoms and the incidence of cardiac dysrhythmias, as one of the disorders of the autonomic system in GERD patients. This phenomenon has been described as a gastrocardiac syndrome. The severity of esophageal inflammation is not related to the dysfunction of the autonomic nervous system itself, given that the presence of vagal dysfunction has been observed in those with or without severe esophageal inflammation. Several studies have suggested that this parasympathetic dysfunction is not only a consequence of esophageal inflammation, but also a major factor in the etiopathogenesis of GERD. Disturbances in autonomic nervous system activity affect the temporary contraction and relaxation of LES, which then causes GERD and affects its severity [15, 16, 22].

Decreased vagal nerve activity, caused by impaired autonomic regulation, appears to be responsible for the dysfunction of LES and the increased transient lower esophageal sphincter relaxation (TLESR) seen in GERD, which results in the increased volume of gastric acid reflux to the esophagus. The exact stimulus and mechanism underlying TLESR are still debatable, although it is currently thought

that TLESR and experimentally induced relaxation of the LES are controlled by neural feedback involving the vagal nerve. The TLESR is triggered by the nerve stimulation of the pharynx, and the relaxation of the LES is triggered by the stimulation of the superior laryngeal and vagal nerves. In addition, gastric distention can also trigger TLESR, but is then inhibited or controlled by vagal efferent and vagal afferent pathways. Most of the sensory neurons that innervate the LES are integrated in the vagal nodular ganglion. There are two things to note before concluding that TLESR is mediated by the vagal pathway. The first is related to vagal efferent fibers that modulate the occurrence of TLESR and the relaxation of the LES; it is still not known whether these two processes are mediated by the same fibers. Second, nonvagal pathways also contribute to the control of the LES. Experimental studies in experimental animals have shown that there is a contribution from spinal afferent innervation in cats, and the relaxation of the LES has also been shown to involve the vagospinal pathway in ferrets. In general, the published literature is consistent with the motion that LES regulation is primarily based on vagal afferent - vagal efferent (vagovagal) reflex mechanisms [15, 16].

In 1980, Heatley *et al.* [16] studied vagal nerve activity in GERD patients by observing changes in pulse rate variability during deep breathing and found that a quarter of these patients had distinct vagal nerve dysfunction, suggesting that vagal nerve dysfunction was the cause of GERD in these patients. The Cunningham *et al.*'s study [15] first demonstrated a high prevalence of autonomic nerve dysfunction among patients with esophagitis diagnosed by endoscopy or abnormal outpatient pH recordings. Abnormalities in parasympathetic tone may cause delayed esophageal transit and abnormal peristalsis. The study by Lee *et al.* [23] found that autonomic tone was lower in patients with endoscopically confirmed (even asymptomatic) esophagitis compared with patients with nonerosive esophagitis (nonerosive reflux disease—NERD). Dobrek *et al.* [24] used heart rate variability (HRV) to measure the strength of high frequency (HF) and low frequency (LF) and found that the GERD group scores significantly lower than the control group at rest. In addition, Lee *et al.* [23] also found that compared with patients with nonerosive reflux disease (NERD), patients with esophagitis (even without symptoms) had lower autonomic nerve function (lower LF and HF strength). Chen *et al.* [21] found that HF strength was significantly lower in patients with erosive esophagitis (ERD) compared to NERD patients and the control group, but LF% and LF/HF ratio were significantly lower in patients with NERD than in ERD patients and the control group.

The study of Wang *et al.* [22] showed that patients with LPR mainly had autonomic dysfunction with relatively worsening vagal nerve function and better sympathetic nerve function. The digestive system is regulated by the autonomic nervous system. Therefore, autonomic dysfunction may lead to an abnormal regulation of gastric peristalsis and upper esophageal sphincter (UES) and LES function, making laryngopharyngeal reflux a risk factor for autonomic dysfunction. Patients with LPR had a significant negative correlation between the strength of HF with RSI and RFS. Higher symptoms and physical scores were associated with worsening vagus nerve function, suggesting that vagal nerve dysfunction is involved in LPR development. Longer disease duration in patients with LPR was associated with lower vagal nerve function, as demonstrated by the analysis of autonomic nerve dysfunction and disease duration. These findings suggest that restoring autonomic nerve function during LPR treatment is critical [16, 22].

Wang *et al.* [22] also showed that autonomic nerve dysfunction is correlated with LPR, and effective treatment needs to be explored. Research by Hu *et al.* [25]

confirmed that patients with anxiety and depression had marked autonomic nervous dysfunction and significantly improved after being treated for anxiety and depression. Chen *et al.* [26] concluded that a decrease in HRV can be used as a psychophysiological biomarker in patients with depressive disorders, and even a very significant decrease in HRV was found in a population of subjects with mixed anxiety and depression disorders. Our observations in outpatient care also observed that some patients with LPR showed signs of mild anxiety and depression [16, 22, 25, 26].

LPR is an inflammatory condition in the upper gastrointestinal tract associated with the direct and indirect effects of exposure to reflux of gastroduodenal contents and can cause morphological changes in the upper aerodigestive tract. The etiology of this disease is multifactorial, the diagnosis is still a challenge in itself, and the pathogenesis aspect has not been conclusively explained. This has an impact on the management of patients and the burden of health financing. Autonomic nerve dysfunction is thought to play a role in the occurrence of LPR. It is known that decreased vagal nerve activity caused by autonomic dysregulation is responsible for GERD, but whether the same pathomechanism associated with autonomic dysfunction occurs in LPR requires further research [25, 27].

4.2 Sleep-disordered breathing (SDB)

Obstructive sleep apnea (OSA) is characterized by an episodic collapse of the upper airway during sleep, resulting in the periodic reduction or pause in ventilation and hypoxia, hypercapnia, or awakening from sleep. The prevalence in the general population is estimated to be 3% in women and 10% in men with ages ranging from 30 to 49 years [28, 29]. Overnight polysomnography is required to document the frequency of respiratory events, apnea, and hypopnea during sleep in OSA diagnosis. Obstructive apnea is the complete (>90%) or nearly complete cessation of airflow for more than 10 seconds during sleep despite ventilation efforts. Hypopnea is a decrease in airflow of at least 30% followed by a decrease in oxygen saturation of at least 3% or awakening from sleep. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. OSA criteria are the occurrence of AHI at least five events per hour. Therefore, traditionally, AHI is categorized based on the number of events per hour. AHI in the mild category is 5–15 AHI events per hour, the moderate category means 16–30 events per hour, while the severe category is more than 30 events per hour [28–31].

Events in which 15 or more AHIs per hour were associated with a decrease in psychomotor speed are equivalent to 5 years of aging. The higher the AHI, the lower the subjective quality of life. Untreated OSA triples the risk of motor accidents compared to the general population. Most importantly, OSA was associated with an increased risk of cardiovascular disease, particularly stroke, hypertension, heart failure, and coronary artery disease, even after adjustment for body mass index (BMI) and other risk factors. In addition, OSA patients also tend to increase the risk of heart arrhythmias, including atrioventricular block, ventricular tachycardia, and sinus bradycardia [29–31].

In healthy individuals, hypoxia (i.e., decreased oxygen levels with an arterial pO_2 of less than 60 mmHg) causes chemoreceptor activation and triggers tachycardia and an increase in blood pressure. Hypoxia and hypercapnia increase the incidence of hyperventilation (resulting in an increased distribution of oxygen to the peripheral blood), and increased sympathetic efferent activity resulting in vasoconstriction to redistribute oxygenated blood flow. Baroreflex activation in healthy individuals

eliminates the increase (reduction) in sympathetic activity caused by hypoxia, which can lead to vagal activation and bradycardia [29, 32, 33].

Convergent evidence obtained from studies with neuromuscular sympathetic nerve activity, plasma catecholamine levels, and analyses of heart rate variability suggests that in patients with OSA, hypoxia and apnea trigger a cascade of excitability that results in an acute elevation of efferent sympathetic activity during sleep when maintained over a prolonged period of time. Over time, it can induce the chronic sustained elevation of the sympathetic outflow regulatory point during wakefulness. This has implications for a higher risk of chronic hypertension, coronary artery disease, and cerebrovascular disease. Excessive sympathetic outflow, in turn, causes baroreflex-mediated cardiovagal efferent activity and bradycardia, atrioventricular block, and ventricular tachycardia, potentially resulting in sudden cardiac death. The incidence of arousal during obstructive apnea is associated with sleep fragmentation and further sympathetic efferent activity, leading to peripheral vasoconstriction and sudden increases in systolic and diastolic blood pressure and heart rate [29, 32, 33].

Upper airway collapse during sleep resulting in obstructive apnea causes changes in intrathoracic pressure resulting in myocardial stretching of the heart chambers and changes in the transmural pressure gradient, particularly affecting the atria. It can also cause atrial fibrillation and other arrhythmias. In addition to hypoxia and apnea, other mechanisms may be associated with sympathetic efferent overactivity that develops in OSA patients. Obesity, apart from mechanically obstructing the airway and causing OSA, is also responsible for increasing sympathetic afferent activity through mechanisms of leptin, insulin, angiotensin, and cytokines. On the other hand, many OSA patients are not obese. Studies with animal models have confirmed carotid chemoreceptor hypersensitivity due to intermittent hypoxia that contributes to the pathogenesis of OSA in humans. Overactivation of the nucleus in the CNS induces neural changes that increase excitatory impulses to the rostral ventrolateral medulla and maintain high sympathetic tone independently of peripheral sensory signals [32–34].

During sleep, the frequency of TLESR decreases because the stimulus is thought to be associated with gastric distension. During a person's sleep, there is no eating or chewing process, resulting in a reduction in saliva production and a decrease in neuromuscular coordination activity in the swallowing process; this will have implications for the lengthening of the esophageal clearance so that there will be a longer contact between the irritant refluxate and the esophageal mucosa (prolonged contact). This phenomenon then underlies a new entity called sleep-related GERD. Although the frequency of TLESR decreases during sleep, transient relaxation has been observed to occur during cortical arousals in patients with sleep-disordered breathing (SDB). These findings also corroborate the results of Gottesmann's study regarding the association of sleep disorders with the incidence of autonomic dysfunction through the modulation of the neurotransmitter gamma aminobutyric acid (GABA). Gottesmann found that TLESR is vagal mediated and can be inhibited by GABA-b. Lang *et al.* found another reflex pathway involved in the occurrence of TLESR when the patient was not in the process of swallowing, namely through the esophageal distention reflex (EDR) [22, 25, 27].

This EDR consists of several subtypes of pathways that can be evoked through pressure inflation-related stimuli (slow air and rapid air stimulation) instead of volume on mechanoreceptors in the mucous or muscular layers of the pharynx, larynx, and esophagus. In the slow air distention pathway, a secondary peristaltic reflex (2P) will occur, which then stimulates the esophago-UES contraction reflex

(EUCR); this pathway will certainly play a role in preventing reflux episodes from occurring. Meanwhile, through the rapid air distention pathway, four other reflex pathways [esophago-UES relaxation reflex (EUSR), esophago-glottal closure reflex (EGCR), esophago-esophageal contraction reflex (EECR), and esophago-hyoid distraction reflex (EHDR)] will be activated and strongly suspected to play a role in the occurrence of belching. Lang *et al.* also found that all of these EDR subtypes were modulated by vagal afferents and could be inhibited by GABA-b, in accordance with Gottesmann's findings. Experimental studies conducted on cats by Hornby showed that not only GABAb was involved, microinjection of GABAa antagonists into the dorsal vagus motor resulted in a 71% decrease in sphincter pressure. This proves that the neurotransmitter GABAa also plays a role in the transient relaxation of the esophageal sphincter [25, 27, 35].

Sleep disturbances in GERD patients have been shown to induce changes in visceral perception and pain threshold. This investigation showed that in GERD patients with sleep disturbances documented by actigraphy, acid-infusion-induced chest pain was markedly exacerbated after three nights of sleep deprivation. These functions are modulated by afferent branches of the vagus nerve. Gottesmann also found that low levels of GABA in the CNS will affect a person's sleep quality. This would have implications for decreasing slow waved sleep and increasing paradoxical sleep (fragmentation and arousals) [35]. These observations prompted Chen and Orr to conduct a study to test the hypothesis that changes in autonomic function play a role in the pathogenesis of GERD. They achieved it by using spectral analysis of heart rate variability during their study's esophageal infusion of 0.1 N hydrochloric acid. This study proves that the infusion of water and acid can cause a decrease in vagal tone in GERD patients compared to normal [36–38].

4.3 Chronic cough (CC)

Cough is the most common complaint of patient admitting to hospital. In the United States, as many as 27–30 million cases of cough are found in primary care each year [39]. Chronic cough is estimated to occur in 10–20% of the general population, and an important cause of morbidity in 3–40% of the population [39, 40]. The coughing process consists of a complex process; there are: (1) afferent pathways: sensory nerve fibers (branches of the vagus nerve) located in the ciliated epithelium of the upper airway; (2) central pathway (cough center): a central coordinating region for coughing that located in the upper brain stem and pons; and (3) efferent pathway: stimuli from the cough center travel to the diaphragm, abdominal wall, and muscles via the vagus, phrenic, and spinal motor nerves. The nucleus retroambigualis of the phrenic and spinal motor nerves transmits these stimuli to the inspiratory and expiratory muscles, while the ambiguous nucleus of the laryngeal branches of the vagus nerve transmits to the larynx [40]. Coughing is a physiological reaction of the body that can produce intrathoracic pressure up to 300 mmHg and particle velocities of up to 800 kilometers/hour. While these pressures and velocities are important on mucus clearance, they are also responsible for many of the complications such as exhaustion, insomnia, headache, dizziness, musculoskeletal pain, hoarseness, excessive perspiration, urinary and fecal incontinence, to rib fractures [41]. Based on cough duration, it is classified into three subtypes: acute (less than 3 weeks, usually due to viral upper respiratory tract infection), subacute (3–8 weeks), and chronic (more than 8 weeks) [39, 40]. Chronic cough is often associated with smoking. Chronic smokers are three times more likely to have a chronic cough than nonsmokers [41]. Chronic coughs

are more difficult to diagnose and require an examination by a specialist for further evaluation.

Sensory neuropathy or autonomic dysfunction of the laryngeal branch of the vagus nerve can also lead a chronic cough manifestation. The autonomic dysfunction of the vagus nerve puts the laryngeal mucosa in a hyposensitive and hypersensitive state. The most common cause of this symptom is laryngopharyngeal reflux (LPR) [42]. Another etiology of neuropathy is viral infection, especially in the upper respiratory tract. However, it is very difficult for the clinician to determine the etiology because of the atypical clinical symptoms and limited diagnostic modalities. Cough can be mediated by the detection of irritant stimuli in the airway by vagal sensory nerve fibers leading to cough induction via the brainstem without any conscious control or regulation. In neurogenic cough, there was an increase of cough reflex at brainstem level or central sensitization [39, 43].

Because of its neurogenic pain-like characteristic, some of the neuromodulator treatments were considered as a potential therapeutic option for neuropathy cough therapy. Neuromodulator therapy such as gabapentin, pregabalin, and amitriptyline, along with other agents such as baclofen and tramadol [44]. The study by Lee and Woo [45] examined 28 patients with suspected recurrent/superior laryngeal nerve neuropathy. All patients were given gabapentin therapy, with an initial dose of 100 mg/day, which then gradually increased to a maximum of 900 mg/day for 4 weeks. Overall, 68% of patient showed improvement of cough complaints and sensory neuropathy after therapy, especially in the group with clear signs of motor neuropathy.

Chronic cough due to post viral vagal neuropathy is one of the conditions that become the differential diagnosis in cases with unclear etiology. This type of cough is included in the neurogenic cough and is one of the symptoms of laryngeal hypersensitivity syndrome. This theory was originally stated by Morrison *et al.* [43], who said that irritable larynx syndrome (ILS) is an individual response against changes in the central nervous system that cause the sensorimotor pathways to be in a hyperexcitable state. These changes are thought to have a multifactorial etiology, but the most common are reflux. However, more than one-third of the patients in this study have had a history of upper respiratory tract infection before the onset of symptoms. Neural plasticity processes that occur as a result of postinfectious nerve injury can inactivate initial afferent nerves from central neurons and then create new pathways or reactivate old synapses. An afferent stimulus will produce a different response due to changes in the expression of ion channels and other receptor, including TRPV-1, which has an important role in regulating nervous excitability by chemical stimuli [44].

4.4 Paradoxical vocal cord movement

Paradoxical vocal cord movement (PVCM) is a laryngeal disorder, an inappropriate adduction of the vocal cords during inhalation and sometimes exhalation that affects respiratory function and serves as a mimicker of asthma. Vocal cord dysfunction can be difficult to treat as the condition is often underpredicted and misdiagnosed as asthma or other airway disorder and causing inappropriate treatment [46].

The vocal cords normally open (abduction) into a V opening, called the glottic chink during inspiration and close (adduction) into a narrower V shape during expiration. The contraction of the posterior cricoarytenoid muscle allows the outward rotation of the arytenoid on the cricoid cartilage opening the airway

during inspiration. Passive relaxation of the posterior cricoarytenoid muscle during expiration, causing adduction of the vocal cords and close the laryngeal airway, with thyroarytenoid muscle movement supports and provides positive pressure at the end of expiration and prevents bronchial collapse [46, 47], while the lateral cricoarytenoid muscle allows inward rotation of the arytenoid on the cricoid cartilage, closing the laryngeal airway during deglutition, vocalization, and expiration.

The term of PVCM is laryngeal dyskinesia when there is adduction of the vocal cords during inspiration, thereby restricting the airway opening leading to episodic dyspnoea, wheezing and/or stridor, so that it is usually mistaken for asthma. Direct visualization by using laryngoscopy of the vocal cords while the patient is having symptoms is the gold standard for diagnosing PVCM [46]. The etiology of PVCM is unclear but has been hypothesized triggered by a psychological, neurological, or physiological component. Laryngopharyngeal reflux, GERD, croup disease, or exposure to toxic inhalants were suspected as PVCM triggers [47]. In a study by George *et al.* [48], from 27 patients diagnosed with PVCM, 66% of the patient also have LPR, which was found through flexible fiber laryngoscopy examination. Another finding on examination is that there was a presence of posterior laryngitis and cobblestone on the posterior pharyngeal wall.

PVCM is defined as voice disorder in the absence of organic pathology and suspected have association with autonomic nervous system (ANS) function. Study of Helou *et al.* [49] found that laryngeal muscle activity, an intrinsic laryngeal muscle (ILM), was increased with activation of the autonomic nervous system due to the presence of acute stress. This study showed that participant's heart rate and blood pressure measures are significantly increased during the exposure of the stress, which represents the activity of autonomic nerve. ILM activity observed was elevated followed by the increase of heart rate and blood pressure due to the stimuli from afferent nerve of the stress. The larynx receives both sympathetic and parasympathetic innervation, which human laryngeal muscle exhibits a response due to ANS activation [49]. Exposure to acids and irritants in the laryngeal area were suspected causes PVCM incidence. Vocal cord dysfunction may be caused by laryngeal hyperresponsiveness, initiated by an initial inflammatory insult and resulting in altered autonomic balance. Inflammatory and irritant stimuli can have tendency to laryngeal narrowing due to laryngeal hyperresponsiveness which will contribute to wheezy breathlessness [50].

A study of Morrison *et al.* [43] stated that irritable larynx syndrome (ILS) is caused by chronic reflux stimulation. In ILS, a process called neural plasticity causes changes in neuronal control of the larynx and other structures due to exposure to irritants. It causes changes in the neuronal control of the larynx and surrounding structures due to exposure to irritants. This explains the changes in the central nervous reaction to certain stimuli. In PVCM, neural plasticity is a response to an irritating process that makes the afferent input work incorrectly and then forms a new connection of the dendrites resulting in inappropriate afferent input response, such as the laryngeal adductor reflex (LAR) [43, 51].

The LAR is also called the glottal closure reflex, which is a protective mechanism of the larynx to prevent material entering the upper respiratory system. The muscle that plays a role in this mechanism is the thyroarytenoid muscle, which responds to mechanical stimuli and chemical irritants in the laryngeal mucosa. LAR is mediated by the brain stem, which is an involuntary reflex innervated by the internal branch of the superior laryngeal nerve as an afferent and the recurrent laryngeal nerve as an efferent component [51]. In patients with LAR disorder, laryngeal hypersensitivity, chronic cough, and vocal cord dysfunction also might be found [43].

Episodes of PCVM can be triggered by the irritation of the laryngeal mucosa, as in tobacco abuse, allergic laryngitis, viral illness, and untreated sleep apnea, making treatment more difficult. Irritation of the vocal cords can be directly caused by rhinosinusitis and the resulting postnasal drip. However, inflammation can also occur indirectly due to the release of inflammatory mediators [47]. Patients with PVCM usually present with shortness of breath (stridor or wheezing) that appears suddenly and worsens rapidly to apnea and aphonia. Complaints appear for a few seconds but can continue for several minutes before disappearing. Attacks can occur at any time, even during sleep. Complaints of wheezing are usually more common during inspiration than expiration [46, 47].

In acute attacks, patients with PVCM can show signs such as upper airway obstruction, namely shortness of breath, stridor, respiratory muscle retraction, difficulty in speaking, and anxiety and even loss of consciousness. Some typical symptoms such as a feeling of suffocation in the neck or throat, more difficult to inhale than exhale, partial response or no response to inhalation [47]. At the time of an acute attack, patients with PVCM may show signs such as upper airway obstruction, namely shortness of breath, stridor, respiratory muscle retraction, difficulty in speaking, and anxiety and even loss of consciousness [52]. Auscultation should be performed on the neck and lungs to exclude lower respiratory disorders, i.e., asthma and other pulmonary diseases. On auscultation of the neck, wheezing or stridor will be found, especially during inspiration [53].

The diagnosis of PVCM requires flexible fiber-optic laryngoscopy as the gold standard, and vocal cord movement is observed when breathing. Typical findings in PVCM are paradoxical movement of the vocal cords, adduction on inspiration, and narrowing of the glottis during acute attacks. Complete adduction of the vocal cords during inspiration with or without formation of a small posterior diamond shaped, known as posterior chink, is the pathognomonic of PVCM. These findings may also be present during expiration [47, 53]. The differential diagnosis of PVCM is laryngeal edema, vocal cord paresis, laryngeal or tracheal neoplasms, subglottic stenosis, aspiration of foreign bodies, laryngomalacia or tracheomalacia, laryngeal granulomas, and laryngeal spasm [54].

Management of PVCM requires a multidisciplinary approach. Mentally support by calming the patient or reassurance can reduce symptoms significantly. The patient is directed to inhale slowly through the nose and exhale through the mouth [46, 55]. There is no standard pharmacologic management of PVCM besides that used to control comorbid conditions. Medical therapy such as benzodiazepines can also be given to patients with PVCM who have an acute attack. The management of chronic PVCM through breathing exercises, supportive counseling, can be effective. Laryngeal control therapy (LCT) given by a speech pathologist can reduce symptoms in the long term [55]. Proton pump inhibitor therapy and lifestyle modifications can also be given to patients with PVCM associated with an irritated larynx due to gastric acid reflux. The recommended PPI that can be given is omeprazole 20 mg or lansoprazole 30 mg 2 times per day for 3–6 months or for child dose of 1 mg/kg/time given two times per day [55].

5. Conclusions

Altered vagal nerve activity caused by impaired autonomic regulation may appear to play a role in the pathogenesis of laryngeal clinical manifestation and have an

impact in person's quality of life. This often leads to high economic and social burdens on patients due to delay in diagnosis, numerous tertiary care referrals, and lack of effective medications. The degree of dysfunction may have correlation with disease severity. Impaired autonomic regulation in the larynx was thought to be responsible for clinical entities, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and paradoxical vocal cord movement (PVCM). Treating the underlying specific conditions and symptoms are needed, and research with a large series of subjects and application of autonomic modulation as a therapeutic target is recommended in the future.

Author details

Syahrial M. Hutauruk*, Elvie Zulka Kautzia Rachmawati and Khoirul Anam
Faculty of Medicine Universitas Indonesia, Department of Otolaryngology Head and Neck Surgery, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

*Address all correspondence to: smarsinta@yahoo.com

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Section 2

Laryngeal Examination

Chapter 2

Laryngeal Examination with Laryngeal Mirror and Laryngoscopy

Rasmika Kanakarajan and Kanakarajan N.K

Abstract

The management of all laryngeal pathologies begin with a simple and traditional examination with laryngeal mirror. Even though the use of mirror is invaluable, the image is often distorted and misleading in seven different ways. Direct laryngoscopy is a sermon on relaxation and does not require any local or general anesthesia in both children and adults. The greatest advantage of direct laryngoscopy is the presence of oblique illumination. This chapter deals with the different angulations of laryngeal mirrors and its seven drawbacks in detail. This also provides a detailed explanation of direct laryngoscopy technique in children and adults with its axioms and clinical application.

Keywords: larynx, laryngeal mirror, mirror angulation, laryngoscopy, video laryngoscopy

1. Introduction

Laryngeal mirror was first discovered by Professor Manuel Gustave Garcia who was a singer, teacher and composer by profession. He initially used a dentist's mirror and sunlight to visualize the larynx to demonstrate the physiology of vocal cords [1]. Later, this technique was used by Ludwig Türck who is a neurologist cum laryngologist. As he was largely unsuccessful, the attempts were then carried out by Dr. Johann Nepomuk Czermak, a physiologist. He made some modifications by using an artificial light source and a concave ophthalmologist's mirror to successfully visualize the larynx. He thus claims to be the first non-laryngologist to visualize a living larynx [2].

Laryngeal mirror is made of stainless steel with a length of 7–10 inch, mirror diameter of 3–8 mm and thickness of 10 mm. An ideal mirror should be angulated to visualize the larynx precisely. The different degrees of angulation can be 30, 45 or 60 degrees. Of these, 45 degree angulation is found to be the most suitable for our clinical use. This angulation can prevent gag reflex and discomfort to the patient as well as provide us with a better picture of larynx. Individuals with short neck may require more angulation.

This can be facilitated by the future development of malleable handles for easy alteration of angulation according to the patient needs.

1.1 Examination of larynx with laryngeal mirror

Position of the patient: The patient should sit back on the chair and head is leaned forwards with flexion of neck and extension of head.

Left index finger is then used to push the upper lip upwards away from the field. Grab the protruded tongue between thumb and middle finger. Rest the little finger on the chin. Defog the mirror using savlon (Chlorhexidine gluconate and cetrimide)/ warm water. Introduce the mirror inside after checking the temperature. Push the uvula backwards with the mirror and visualize the epiglottis. The glottis will appear black as it is not illuminated. Make a slight tilt with the mirror to visualize the entire larynx (**Figure 1**).

The training for laryngeal examination using a mirror can be made possible with the help of a laryngeal model. The laryngeal model can be made using acrylic sheeting, cardboard or plywood. Such training of students using artificial models was found to be very helpful for easy diagnosis and better understanding of anatomy [3].

The main advantage of mirror laryngoscopy when compared to endoscopic examination is the 3D image visualized via mirror, thereby avoiding any chance of missing early lesions of larynx especially in vestibule or ventricle where the mucosa may be intact. Other advantages are mirror is inexpensive, easy to use and less time consuming.

A prospective randomized crossover trial was conducted by Dunklebarger et al. to compare video rigid laryngeal endoscopy and laryngeal mirror for examination of larynx in 43 patients [4]. All patients were subjected to single attempt with both methods in alternating order without any topical anesthetics. Each patient was asked to rate the level of comfort and gagging from 1 to 10 for each technique (1 indicates no discomfort/gagging and 10 indicates severe discomfort/gagging). Patients were also asked if they found the video recording of examination useful and which technique they preferred. The examiner also checked the level of extend of examination with each technique and recorded it from a scale of 1 to 6 with 6 indicating complete visualization. The study concluded that examination with 4 mm 30 degree rigid endoscope was better than mirror examination in terms of comfort and extend of visualization. Majority of the patients also preferred rigid endoscopy and found the video recording useful.

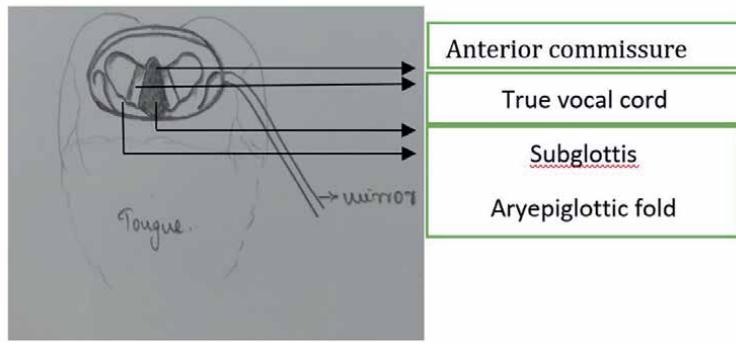

Figure 1.
Laryngeal view with mirror.

Barker et al. conducted a study to compare the success rate and diagnostic accuracy between laryngeal mirror and rigid rod examination of larynx [5]. Success rate with indirect laryngoscopy was 52% whereas, that of rigid rod examination was 83%. The study concluded that laryngeal mirror is an useful screening tool, but rigid rod adds more diagnostic accuracy.

In the study conducted by Grabas et al. to determine the relevance of laryngeal mirror in the examination of larynx and nose, 82% of success rate was found with laryngeal examination [6].

1.2 Disadvantages of laryngeal mirror

The image seen in laryngeal mirror can mislead us in seven different ways.

Even though the plain mirror used in the instrument is round in shape, the image appears to be oval. This will cause a reduction in the anteroposterior dimension or along the vertical axis. As a result of this distortion, the cords appear shorter by about one third of its actual length but its transverse diameter remains the same.

Mirror produces an inverted image. i.e. left cord remains on left side of the patient but anterior commissure is seen posteriorly.

Mirror image can alter the depth perception. Vocal cords appear to be 1–2 cm away from the mirror. But the actual distance is around 6 cm.

Mirror image can cause distortion such that a small vocal cord lesion may appear much posterior than its actual position.

Overhanging ventricular band may be misinterpreted as outer border of vocal cord.

Anterior commissure may be hidden due to the overhanging epiglottis.

Ventricle may be hidden due to the overhanging ventricular band.

Hence, it is quite clear that mirror laryngoscopy when performed by an experienced doctor is always worthy when compared to the other techniques. This technique will never become a lost art in the era of modern medicine even though it has a few demerits [7].

2. Direct laryngoscopy

The first laryngoscope was described by Bozzini in 1805, but its usage was first reported only in 1852 [8]. Since then, a wide range of modifications were introduced and different types of laryngeal blades were made. Even then, the use of rigid laryngoscope, indirect laryngoscope, flexible laryngoscope and video laryngoscope remains fundamental to all ENT surgeons worldwide. This can be attributed to its ease of use, low cost, better visualization with less patient discomfort and complications and easy availability. A laryngoscope has got a handle, blade and a light source. The light source can be diode emitting or fiberoptic light source.

Suspension laryngoscopy with rigid laryngoscope is often used in laryngeal examination for diagnostic and therapeutic purpose. Direct laryngoscopy (rigid or flexible) can be used for phonosurgeries like excision of vocal cord cyst, polyp, excision/biopsy of laryngeal growth, thyroplasty, percutaneous tracheostomy or laryngeal reinnervation surgeries. Direct laryngoscope helps in providing the anatomic and pathologic details in its original form, color and relationship. The main advantage is the provision of oblique illumination due to the presence of distal source of light on its one end. The color should always be adjusted to the

same intensity to avoid mucosal blanching due to over illumination. The only absolute contraindication to direct laryngoscopy is disease of cervical spine other than uncontrolled systemic illness.

Video laryngoscope provides a superior view than direct laryngoscope. Numerous types are commercially available in market today. The main disadvantage it that it has a blind spot creates when endotracheal tube is inserted. But its widespread use by surgeons can be attributed to its robust and ease of use with minimal set up time and short learning curve. American Society of Anesthesiologists has added video laryngoscopes to the practice guidelines in management of difficult airways [9].

2.1 Anesthesia

No anesthetic, local or general, is ideally required in both adults and children to perform laryngoscopy if the surgeon is skilled and the teamwork is well coordinated. For this, patient should be relaxed completely or else, examination will be difficult. If required, 10% lignocaine spray can be used as local analgesic. One puff of 10% lignocaine contains 10 mg and 1 ml contains 100 mg of lignocaine. Two to three puffs should be sprayed to the base of the faucal pillar and pharyngeal wall and wait for few minutes for the effect. In older days, cocaine drops were frequently used for anesthetic effect.

2.2 Premedication

When performed under local anesthesia, premedication is highly efficient. 1 ampule of Phenergan or pethidine 25 mg can be given as IM or IV along with IV atropine or glycopyrrolate to reduce the secretions. Atropine 0.6 mg or Glycopyrolate 0.01 mg/kg is the dosage which should be given 10 minutes prior to the procedure.

2.3 Technique

Position of the patient: "sniffing the morning air" position or flexion of neck and extension of head. This is attained by making the patient to lie down in supine position with head raised 10 cm above the body level using a head pillow.

Steps of introducing a laryngoscope:

Retract the upper lip using the right index finger.

Introduce the scope along the right side of anterior two thirds of tongue.

Once the posterior third of tongue is reached, push the scope towards the midline and visualize the epiglottis.

Push the scope towards the posterior pharyngeal wall and insert posterior to the epiglottis to 1 cm down into the larynx (**Figure 2**).

When performed under local anesthesia, often larynx will be in spasm which is not seen with general anesthesia.

If anterior commissure is not seen, head elevation can be increased or press over the thyroid cartilage externally with the index finger.

Visualize the entire larynx and then while pulling the scope out, check for hypopharyngeal region.

Structures to visualize while performing direct laryngoscopy.

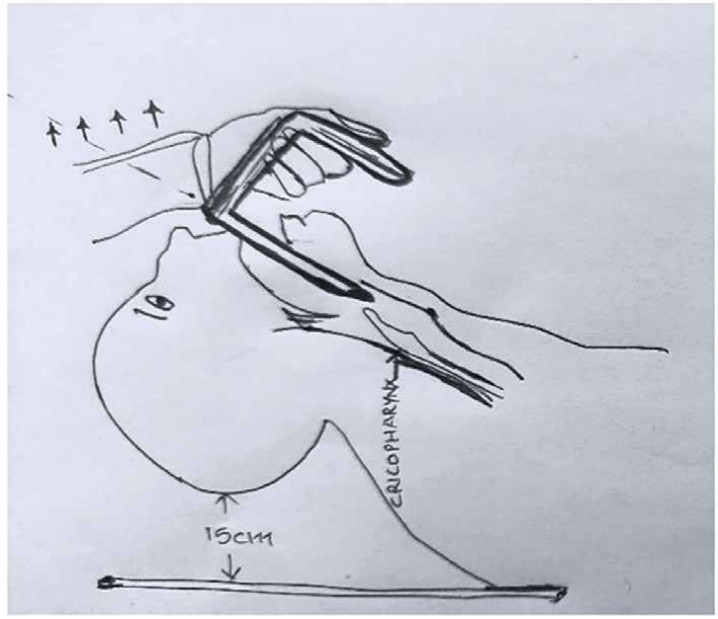

Figure 2.
Examination with direct laryngoscope.

- Tongue
- Base of tongue
- Pharyngeal wall
- Epiglottis
- Vallecula
- Glossoepiglottic fold
- False vocal cord
- Anterior commissure
- Posterior commissure
- Ventricle
- Subglottis
- Anterior wall of trachea
- Arytenoids

- Aryepiglottic fold
- Pyriform fossa
- Movement of vocal cord and arytenoids

2.4 Axioms of direct laryngoscopy

Laryngoscope should always be held in left hand.

Surgeon's right index finger is used to retract the patient's upper lip.

Maintain the right patient position with head in midline and flexed only at atlanto-occipital joint.

Laryngoscope should be introduced along the right side of tongue. When the posterior third of tongue is reached, scope should be directed towards the midline. Do not proceed into the larynx without visualizing the epiglottis.

Care should be taken not to insert the scope deeply or else this may hide the epiglottis.

Even after visualizing epiglottis, scope should not be inserted too deeply.

Laryngeal exposure is obtained by lifting forward the epiglottis.

Do not mistake aryepiglottic fold for epiglottis.

If the laryngoscope is long, secretions may tickle down the trachea causing cough. This should be avoided by suctioning adequately.

In children, cartilage is more flexible and larynx will be seen only with a deep breath.

2.5 Advantages

Cords will appear longer than it seemed in the mirror and may not be pearly white in appearance.

True depth perception.

Ventricular bands appear as folds rather than lumps.

Video laryngoscopy is better than direct laryngoscope for glottis visualization and airway assessment/intubation [10, 11]. Whereas, in the systematic review and meta-analysis conducted by Savino et al. states that in physicians with adequate experience with DL, VDL did not contribute to any additional success and may even lead to worsening experience. However, in nonphysician intubators with less DL experience, VDL will provide more benefit [12].

The study conducted by Schild et al. showed that use of an hyperangulated video laryngoscope with usage of modified flexible instruments can be cost effective and minimally invasive alternative in cases of difficult laryngeal exposure [13].

In a study conducted by Boles et al., flexible distal chip laryngoscopy was compared with rigid telescopic laryngoscopy in terms of image quality and diagnostic ability in 18 patients [14]. All 18 adult patients were subjected to both the techniques and the video recorded were analyzed to find the statistical significance in the parameters. The study concluded that rigid laryngoscopy was superior in image quality in terms of color fidelity, resolution and vascularization with better visualization of abnormalities.

A randomized crossover study to compare the patient experience between rigid and flexible laryngoscopy was conducted by Clark et al. in adult patients [15]. They

also concluded that flexible scopy was associated with more discomfort and pain than rigid laryngoscopy.

A study was conducted by Swapna et al. to compare the difference in the assessment of posterior glottis chink between rigid laryngoscope and flexible nasopharyngolaryngoscope [16]. 108 patients were subjected to both the techniques of laryngeal examination and posterior glottis chink score was assessed. Score 0 being closed glottis and score four being most open glottis. The study concluded that females had higher posterior glottis chink score and rigid laryngoscope was more efficient in assessing the posterior glottis chink, but the difference was not very significant.

In contrary to this, a retrospective study was conducted by Omokanye et al. to determine the diagnostic efficacy of flexible laryngoscope in 360 patients and was compared with DL. The results showed that the diagnostic accuracy was comparable to DL and is more statistically significant when compared to the above mentioned studies [17]. Thus, the usage of flexible laryngoscopy in OPD setting and DL in theater setting with anesthesia is more reasonable. Flexible laryngoscopy is a simple, safe and cost effective procedure which can be performed with simple head extension, sniffing position or sitting position [18].

A comparative study between rigid and flexible fiberoptic laryngoscope was done by Handler to examine the pediatric larynx [19]. Flexible fiberoptic laryngoscope was chosen as the preferred technique to examine airway dynamics. Rigid laryngoscope was preferred in cases of laryngeal or tracheal surgery. This was due to the ease of use and better image perception as a result of magnification. Hence it is clear from the above mentioned studies that flexible laryngoscope is easy to use and provides good image perception and will be a better option than rigid laryngoscope in OPD settings. Yet, more studies with larger sample size have to be conducted to prove its efficacy.

2.6 Disadvantages

Direct laryngoscopy is an essential tool for phonosurgery. But several parameters can limit its use by restricting the visibility. These include short and stiff neck, obesity, retrognathia, macroglossia and cervical spine pathology limiting neck extension. This can even hinder the process of intubation. The incidence of DLE and difficult intubation is around 1–4% [20]. Hence, the usage of direct laryngoscope in OPD setting without anesthesia is obsolete and is replaced by flexible laryngoscope.

2.7 Complications

Excess application of force while inserting the scope can damage the cartilages or may cause mucosal injury leading to bleeding. Bleeding can in turn obscure the view.

Laryngospasm is another complication if not performed under sufficient anesthesia or due to excess manipulation.

If the correct size of scope is not used, complete visualization of larynx may not be possible.

Resting the scope on the upper jaw or tooth can lead to dental damage and hence should be avoided.

There are different types of rigid laryngoscopes and suspension laryngoscope.

Rigid endoscope can be of different angulations: 45 degree, 70 degree, 90 degree, 110 degree. Of these, 70 degree scope is commonly used.

Color codes for these endoscopes are:

- 0 degree—Green.
- 30 degree—Red.
- 45 degree—Black.
- 70 degree—Yellow.
- 90 degree—Blue.
- 110 degree—Grey.

The different types of suspension laryngoscopes include:

a. Vaughn.

b. Zeitel.

c. Kleinsasser.

d. Bercy-Ward.

e. Bouchayer.

f. Lindholm.

Among these, Vaughn's and Zeitel's is preferred for glottic and anterior commissure exposure as it has a triangular distal opening.

2.8 Clinical applications

Vocal fold surgery

- Mucosal and submucosal excision of lesions
- Stripping of vocal folds
- Lysis of synechiae and adhesions
- Vocal fold medialization/augmentation

Foreign body removal.
Laryngeal framework surgery.
Laryngotracheal stenosis—Stent/Keel placement.
Percutaneous tracheostomy.
Assists Intubation.
Diagnosis and treatment of Hypopharyngeal lesions.
Zenkers diverticulum.

3. Conclusions

Rigid direct laryngoscopy in an OPD setting without LA or GA is out of favor in the present context. Instead, it is being replaced by flexible video laryngoscope in an OPD setting, which is more compatible for the patient and gives excellent magnified images which can be photographed or videorecorded for documentation and teaching. Rigid laryngoscope with angulated and self-expanding blades are reserved for microlaryngeal surgical procedures. The only disadvantage of all video endoscopes compared to laryngeal mirror is the lack of 3D perception i.e., lack of depth perception. This can lead to failure to diagnose certain laryngeal lesions which can be easily picked up using a laryngeal mirror. Hence, laryngeal mirror will always serve to be an invaluable instrument for ENT surgeons.

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Nil.

Appendices and nomenclature

Nil.

Abbreviations

DLE	Direct laryngeal endoscopy
DL	Direct laryngoscopy.
VDL	Video direct laryngoscopy.

Author details

Rasmika Kanakarajan* and Kanakarajan N.K
Department of ENT, Holy Cross Hospital, Kollam, Kerala, India

*Address all correspondence to: rasmikakraj93@gmail.com

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Section 3

Reflux Associated Problems

Chapter 3

Updates on Laryngo-Pharyngeal Reflux (LPR) and Its Management

Hardip Singh Gendeh and Balwant Singh Gendeh

Abstract

Laryngo-pharyngeal reflux (LPR); esophageal reflux; pharyngolaryngeal reflux; or reflux laryngitis refers to the backflow of acid from the stomach to the upper aerodigestive tract of the larynx and pharynx. Repetitive reflux of these contents may lead to LPR. It has been estimated that half of the otolaryngology patients with laryngeal and voice disorders have LPR. The pattern of reflux is different in LPR and gastroesophageal reflux. LPR usually occurs during the daytime in the upright position, whereas gastroesophageal reflux disease more often occurs in the supine position at nighttime or during sleep. Laryngeal edema is an important indicator of LPR that is most often neglected. LPR was previously deemed a controversial topic in laryngology but is now clearer with a better understanding of the pathogenesis. Diagnosis is made based on symptoms, and laryngoscopy aided with investigations and confirmed the response to treatment.

Keywords: laryngo-pharyngeal reflux, esopharyngeal reflux, pharyngolaryngeal reflux, reflux laryngitis, management, updates

1. Introduction

Laryngo-pharyngeal reflux (LPR); esopharyngeal reflux; pharyngolaryngeal reflux; or reflux laryngitis refers to the backflow of acid from the stomach to the upper aerodigestive tract of the larynx and pharynx. The larynx has a neutral ph of 7 compared to the acidity of the stomach at ph 1.5 to 2. As a result, whenever stomach contents encounter the larynx, the laryngeal trauma caused by reflux contents often consist of digestive enzymes, such as pepsin, bile salts, and pancreatic enzymes. Repetitive reflux of these contents may lead to LPR [1].

Gasto-esophageal reflux disease (GERD) on the other hand refers to the retrograde flow of gastric contents into the esophagus. Cherry et al. (1968) first suggested LPR being caused by GERD in three patients with persistent contact ulcers of the larynx, having shown reflux peptic esophagitis. These patients had reflux from the esophagus to the pharynx *via* the cricopharyngeal when studied using a barium swallow. Although they did not present with symptoms of GERD, further assessment and history revealed the possibilities of GERD [2].

There is still a debate about whether LPR is a subset of GERD because naturally for LPR to be present, gastric contents will first have to reflux into the esophagus prior to reaching the pharynx and larynx superiorly. Some have argued that GERD

and LPR are separate entities as some reflux into the esophagus may occur and the esophagus is more forgiving to the acidic contents of the stomach as compared to the pharynx and larynx. A patient with reflux may have symptoms of LPR but not GERD. On the contrary, patients with significant GERD without typical symptoms of GERD may present as LPR. These are the cohort of patients who will present to the Otorhinolaryngology specialty for laryngeal symptoms instead. Fraser et al. (1994) have suggested that then laryngeal symptoms (primarily hoarseness) now known as LPR were symptoms of GERD rather than LPR alone. Upon treatment with proton pump inhibitors, these patients report improvements in GERD but not LPR [3].

Some authors have suggested that LPR is not GERD and *vice versa*. Therefore, this chapter explores the causation, symptoms, examination findings, and treatment of LPR and why it does exist.

2. Cause and pathophysiology

Two mechanisms have been proposed for causing LPR [3]. They are as follows:

1. **Gastric reflux at the lower esophagus stimulates a vagal reflex.** This leads to coughing and throat clearing, eventually leading to laryngeal symptoms. Therefore, in this theory, there is no direct insult to the laryngeal mucosa by peptic acid contents.

2. **Gastric reflux bypasses the upper esophageal sphincter causing a direct insult to the laryngeal mucosa.** This has been difficult to prove as pH studies involving a pharyngeal problem have been challenging.

Based on the Montreal Criteria, LPR is defined as the reflux of gastric contents into the esophagus, resulting in symptoms and complications, such as esophagitis, which may develop into a Barrett's esophagus [4]. A patient with LPR may be asymptomatic of GERD symptoms and may fail to meet the diagnostic criteria of GERD. It is estimated that up to 44% of patients with LPR may have a normal esophagogastroduodenoscopy (OGDS) [5, 6]. Therefore, this suggests that LPR and GERD are two separate diagnostic entities, and one may occur independently without the other [7].

Lechien et al. (2020) have highlighted gray areas in the pathophysiology of LPR. Among them is the role of bile salts, which have been shown to be the route of a reflux content causing inflammation to the laryngopharynx. Gastric reflux may contain bile. Little has been done to investigate this among humans. The use of prolonged proton pump inhibitors has been shown to alter the pharyngeal microbial flora, another factor that needs to be investigated as a causative factor. Wang et al. (2019) found a significant correlation between autonomic nerve dysfunction among 81 patients with suspected LPR. There was no correlation between vagal dysfunction and LPR [8]. Stress may upregulate sympathetic nervous system activity, therefore altering the autonomic nervous system and resulting in LPR. Sympathetic activity is believed to be a known cause of a transient relaxation of esophageal sphincters [9].

Patients with LPR are said to have less carbonic anhydrase enzyme, which secretes bicarbonate [10–12], resulting in less bicarbonate content, which is an alkali to neutralize the refluxed gastric contents. Acidity plays an important role. The gastric mucosa has a pH of 1.5 to 2.0, while that of the laryngopharynx is neutral. As little as three episodes of reflux of gastric contents in a week to the laryngopharynx decreases

its pH to a more acidic environment, thus traumatizing the laryngopharynx [11, 12]. The pH of 4.0 is sufficient to traumatize the larynx [13].

Some authors have postulated the role of nonacid reflux, whereby other gastric contents, such as pepsin, are the contributing factor [11, 14]. Symptomatic patients have been shown to have nonacid reflux in a week *via* impedance monitoring. Pepsin may have refluxed and deposited at the laryngopharynx, which is neutral. The presence of acid *via* hydrogen ions from another episode of acid reflux or diet then activates the pepsin enzyme, resulting in intracellular damage [14].

It has been estimated that half of the otolaryngology patients with laryngeal and voice disorders have LPR [15]. The pattern of reflux in LPR and gastroesophageal reflux may vary. LPR usually occurs during the daytime in the upright position, whereas gastroesophageal reflux disease more often occurs in the supine position at nighttime or during sleep. Laryngeal edema is an important indicator of LPR that is most often neglected. Ambulatory 24-h double pH-probe monitoring is the gold standard diagnostic tool for LPR. Besides, gastric mucosa, and laryngeal H pylori have been shown to precipitate GERD. 57% of LPR patients have H pylori. Laryngeal acid and pepsin sensitivity are greater in oropharyngeal mucosa than in esophageal mucosa and this constitutes the main difference between LPR and GERD pathophysiology. *H. Pylori* is found in many sites, including laryngeal mucosa and inter-arytenoid region; however, the importance of this colonization and its effects on disease progress and treatment outcome is yet to be identified with prospective clinical studies [16].

Obesity, smoking, and alcoholic lifestyle changes are contributing factors to GERD, LPR, or both. Smoking and alcohol may result in the worsening of GERD or cause direct trauma to the laryngeal mucosa, thus increasing the severity of LPR symptoms. Obesity simply increases intra-abdominal pressure, increasing the likelihood of GERD or silent GERD.

3. Symptoms

Koufman studied the severity of laryngeal injury in 250 patients with suspected GERD with 24-hours ambulatory esophageal monitoring. In total 197 (81%) of patients had double monitoring with the second probe being placed at the laryngeal inlet at the laryngopharynx. Sixty-one patients had reflux laryngitis. The study revealed that the commonest laryngeal symptoms of patients with suspected GERD were hoarseness, cough, globus sensation, and frequent throat clearing, indicating a possible silent GERD. Among them, only 43% had GERD symptoms of heartburn or acid regurgitation. This differentiates LPR from GERD, whereby heartburn and acid regurgitation are GERD-specific.

Other less specific symptoms are persistent sore throat, excessive laryngeal mucus, dysphagia, and halitosis [17]. The significant LPR has been associated with rhinology symptoms, where the severe reflux content reaches the nasopharynx, thus irritating the nasal mucosa. Pepsin has been found within the epithelium of the inferior turbinate's glandular mucosa and nasal secretions among patients with chronic rhinosinusitis with or without nasal polyposis [18]. A thorough history is indicated to identify a postnasal drip, causing laryngeal irritation and chronic cough among patients with rhinitis symptoms. Nasal endoscopy is often beneficial to ascertain the presence of posterior choanal secretions. LPR may manifest as other laryngology diagnoses, such as subglottic stenosis and laryngeal malignancy. Muscle tension dysphonia and laryngeal spasms may occur too [19].

Hoarseness
Frequent throat clearing
Globus pharyngeus
Chronic cough

Table 1.
Common symptoms of LPR.

Hoarseness can be caused by a variety of laryngeal pathology. It is predominant in LPR patients and should be considered in patients with hoarseness for more than 3 months [17]. LPR or GERD associated hoarseness is a change in voice that tends to occur upon waking up and improves with the day. It was initially thought that a supine position during sleeping encourages gastric reflux into the larynx, resulting in hoarseness, which shall improve upon resuming an upright position. However, Ozturk et al. (2006) have proven that most patients recorded LPR in the upright position as opposed to supine [17, 20]. Koufman et al. have shown that LPR patients have daytime refluxes [13]. Throat clearing can be abusive to the larynx, causing further trauma. Globus pharyngeus is the feeling of a lump in the throat akin to a foreign body sensation. This is unlike odynophagia, which is pain on swallowing. Laryngeal irritation may lead to a cough.

There has been great debate on what is an acceptable LPR episode. A range of 1–4 LPR episodes a day has been given to cause symptomatic LPR [17]. Healthy and asymptomatic individuals of LPR are said to have one episode of LPR in a day [17]. The determining factor of LPR symptoms is its severity where symptomatic individuals may present to the primary care physician or Otorhinolaryngology clinic for treatment. Thus, symptomology alone is inadequate for the diagnosis of LPR. The common symptoms of LPR are listed in **Table 1**.

4. Investigations

The above symptoms are nonspecific to LPR and can be associated with many other ENT pathologies and several investigative procedures should be performed to assist in the diagnosis of LPR.

4.1 Laryngoscopy

Laryngoscopy is a must for patients presenting with laryngeal symptoms, which can be performed *via* a rigid or flexible laryngoscopy. Rigid laryngoscopy with 70 degrees Hopkins scope may be uncomfortable but provides a good view of the larynx. Flexible laryngoscopy to a camera head can be performed through the nose known as a flexible nasopharyngolaryngoscope. Newer video laryngoscopy with a camera at the tip of the flexible scope does provide clearer images. Video chromatography has been useful in the diagnosis of LPR [21]. The most common findings among patients with LPR as documented in the reflux finding score (RFS) are [22]:

1. **Posterior commissure hypertrophy:** It is the most common finding in 85% of individuals with LPR. It can be classified into

    a. **Absent:** Cuneiform cartilage is visualized.

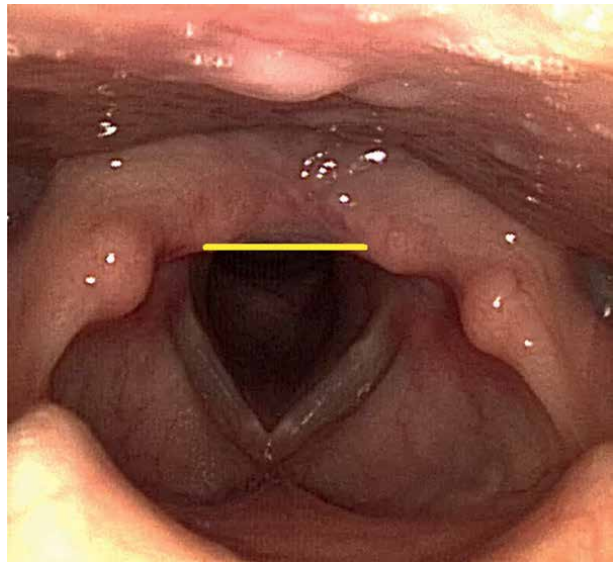

Figure 1.
A moderate posterior commissure hypertrophy with a horizontal line (yellow) at the posterior larynx.

b. **Mild**: Mustache-like appearance of the posterior commissure.

c. **Moderate:** Horizontal line at the posterior larynx (**Figure 1**).

d. **Severe:** More than a horizontal line obliterating part of the posterior segment of the laryngeal inlet.

2. **Ventricular obliteration:** This occurs in 80% of LPR patients. Edema of the true and false cords causes this space to become obliterated; it is further divided into a partial obliteration (whereby the ventricles are partially obliterated with a remaining view of the true cords beneath) and complete obliteration, whereby both the false cord and true cord are edematous, completely obstructing the view of the ventricle in between (**Figure 2**).

3. **Pseudosulcus Vocalis:** Also known as subglottic edema extending from the anterior to the posterior aspect of the larynx and may appear as a double line at the medial free border of the true cords. Pseudosulcus vocalis extends all the way posteriorly throughout the whole length of the vocal fold (**Figure 3**) and it differs from true sulcus vocalis that stops at the midpoint of the vocal fold.

4. **Laryngeal erythema:** Although nonspecific, redness of the larynx can be appreciated, which may be diffuse involving the larynx or confined to the arytenoids. However, this is dependent on image quality, light source, and operator (see **Figure 4**).

5. **Vocal fold edema**: It can be classified into

a. **Mild:** Slight edema

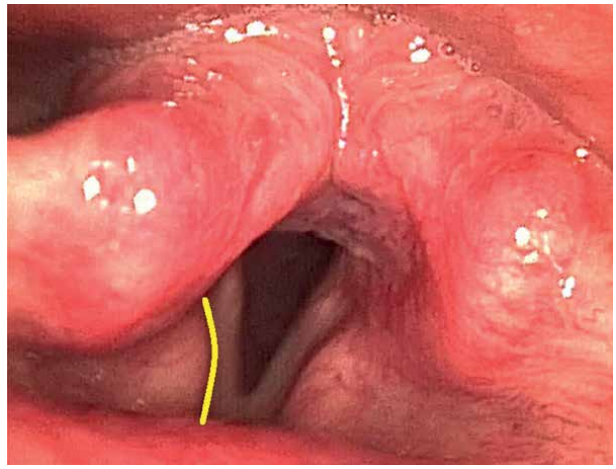

Figure 2.
Edematous false and true cords with partial obliteration of the ventricles (yellow line). There is also bilateral arytenoid erythema.

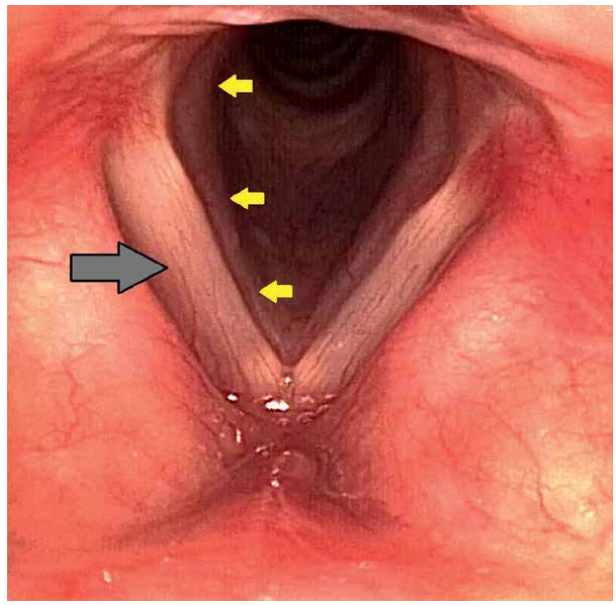

Figure 3.
Pseudosulcus extending posterior (yellow arrows) throughout the length of the true cord (gray). The same appears on the contralateral side.

b. **Moderate:** More perceptible than mild.

c. **Severe:** Edema is appreciated as a sessile swelling involving the whole vocal fold.

d. **Polypoidal**: More than severe that gives rise to a bulky polypoidal appearance.

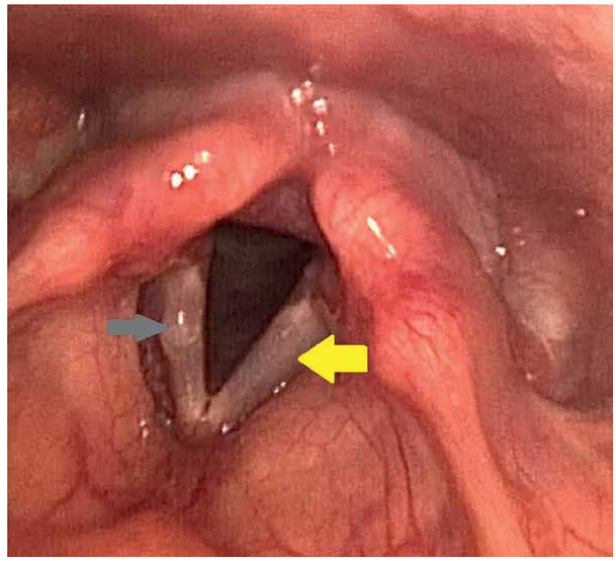

Figure 4.
Edema of the true cords (yellow arrow) bilaterally with thick endolaryngeal mucus at the right midsection of the true cord (gray arrow). The secretions disappeared upon asking the patient to cough.

6. **Diffuse laryngeal edema:** The size of the airway is compared relative to the size of the larynx and is classified into mild; moderate; and severe obstruction. The authors find this classification vague and subject to the interpretation of the operator (**Figure 5a, b**). The above 1–5 scores may contribute to diffuse laryngeal edema.

7. **Granulation tissue:** Granuloma may be present anywhere within the larynx (**Figure 6**).

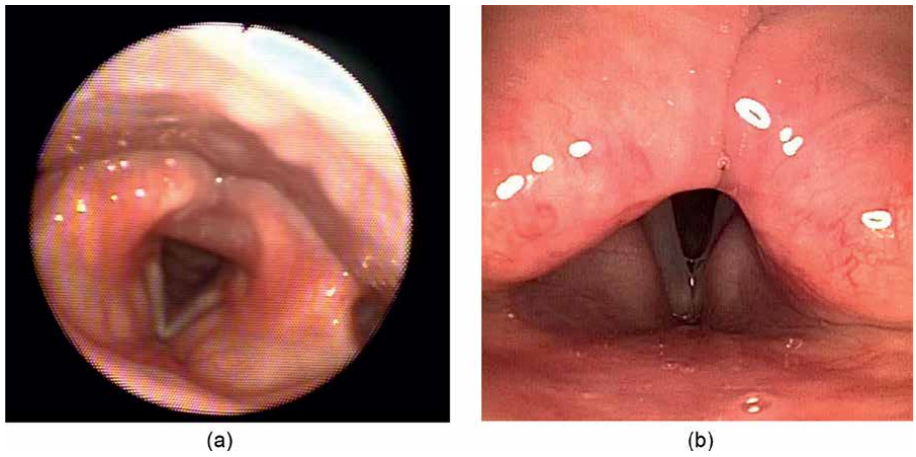

Figure 5.
a: Appreciate the diffuse edema of the supraglottic and glottis structures. There is also ventricular obliteration and posterior commissure hypertrophy. b: Diffuse laryngeal edema, ventricular obliteration, thick endolaryngeal mucus, and supraglottic squeeze during vocalization. As a result, the true cords are partially visualized.

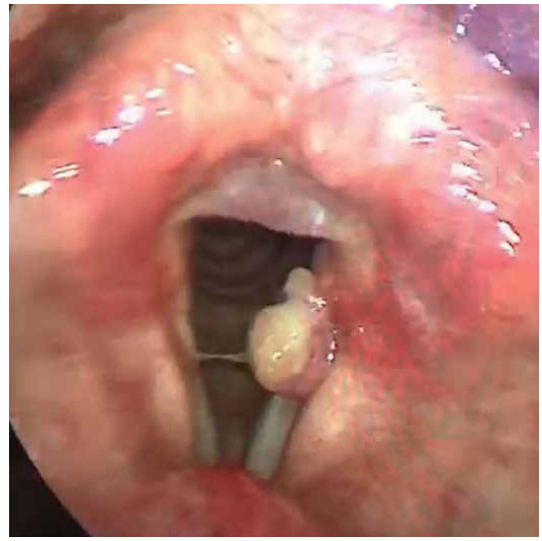

Figure 6.
Granulation tissue from the left true cords in a patient with dysphonia. There is severe posterior commissure hypertrophy extending into the airway. Also, bilateral ventricular obliteration. The patient was a singer and had significant symptoms of LPR.

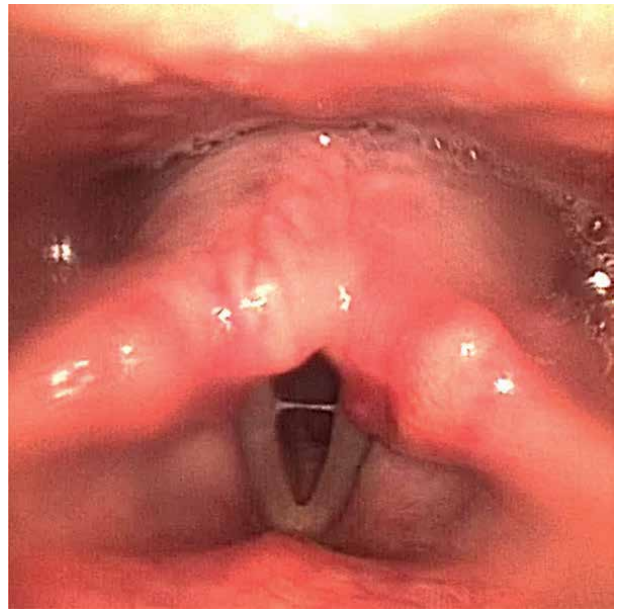

Figure 7.
Thick endolaryngeal mucus across the posterior third of the true cords. There is also edema of the true cords.

8. **Thick endolaryngeal mucus:** This can be appreciated as a horizontal mucus line across the larynx or thick clear secretions within the larynx (**Figure 7**).

Laryngoscopy is a good opportunity to rule out other hypopharyngeal and laryngeal causes of LPR symptoms. It is important to examine the nasal passageway *via* nasal endoscopy. Look out for signs of rhinitis and secretions within the postnasal choana,

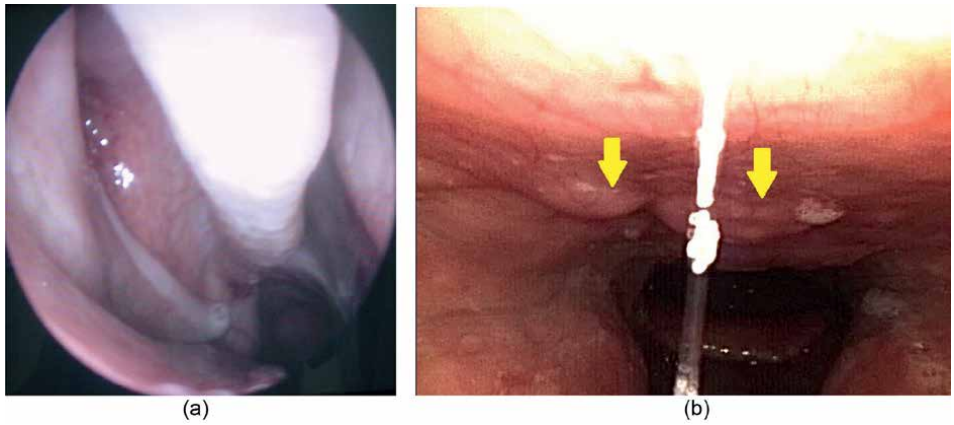

Figure 8.
a: Nasal endoscopic view of the right nose showing mucopurulent discharge from the maxillary ostium draining into the nasopharynx as a postnasal drip (PND). b: FNPLS of the posterior pharyngeal wall (arrows) from the nasopharynx overlooking the oropharynx inferiorly. Appreciate the secretions at the nasopharynx and granular posterior pharyngeal wall. The patients should be examined for rhinitis and a postnasal drip.

which may contribute to posterior nasal drips, resulting in frequent throat clearing and mimicking signs of LPR. They may be concomitant rhinitis with significant postnasal drip and LPR, where rhinitis also needs to be managed (**Figure 8a, b**).

4.2 Esophageal pH monitoring

Esophageal monitoring with a pH probe is the gold standard for identifying gastric acid reflux. LPR is confirmed when pH at the distal esophageal sphincter is less than four for more than 24 hours [20]. A distal esophageal probe is often placed 5 cm above the lower esophageal sphincter to allow for swallowing and prevent displacement into the stomach. Multichannel intraluminal pH monitoring is useful in detecting both acid and nonacid reflux. As, yet, there has been no absolute agreement on pH value that is acceptable to diagnose LPR. There has also been a debate on where to apply the probe for proximal pH monitoring at the hypopharynx, where a fixed double sensor probe is positioned at the hypopharynx will cause an inaccurate position in the distal esophagus and *vice versa* [23]. A dry proximal probe or ingestion of acidic food may result in a pseudo reflux. On the contrary, the reliability of an upper probe in diagnosing LPR is questionable. The presence of acid distal to the upper esophageal sphincter may not represent the same scenario proximal to it within the hypopharynx as the proximal esophageal sphincter itself acts as a barrier to gastric reflux [23]. Some authors have suggested the use of a triple sensor; first proximal; second distal to the upper esophageal sphincter; and third proximal to the lower esophageal sphincter [23]. It has been difficult to correlate the reflux severity and the intensity of LPR [11, 20].

4.3 Reflux symptoms index

The Reflux Symptoms Index (RSI) is a self-administered nine-item outcome for the diagnosis of LPR, which can be completed in less than 1 minute during a consultation. It has a maximum total score of 45 with each nine questions ranging from 0 (no symptoms) to 5 (severe symptoms). It has been validated and shown to be reproducible when compared with Voice Handicap Index (VHI) pre and 6 months posttreatment among patients with LPR [24]. Those with 5 points or more improvements in

Within the last month, how did the following problems affect you?	0 = no problem					
Circle the appropriate response.				5 = severe problem		
1.Hoarseness or a problem with your voice	0	1	2	3	4	5
2.Clearing your throat	0	1	2	3	4	5
3.Excess throat mucus or postnasal chip	0	1	2	3	4	5
4.Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5.Coughing after you ate or after lying down	0	1	2	3	4	5
6.Breadline difficulties or choking episodes	0	1	2	3	4	5
7.Troublesome or annoying cough	0	1	2	3	4	5
8.Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9.Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
			Total			

Table 2.
Reflux symptoms index (RSI).

Subglottic edema	0 = absent 2 = present
Ventricular	2 = partial 4 = complete
Erythema/hyperemia	2 = arytenoids only 4 = diffuse
Vocal fold edema	1 = mild 2 = moderate 3 = severe 4 = polypoid
Diffuse laryngeal edema	1 = mild 2 = moderate 3 = severe 4 = obstructing
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing
Granuloma/granulation tissue	0 = absent 2 = present
Thick endolaryngeal mucus	0 = absent 2 = present

Table 3.
Reflux finding score (RFS) [22].

RSI correspond to a likely 11 points improvement with VHI [24]. Since normal healthy individuals may have reflux too, a score of >13 is considered abnormal. Its limitations include failure of representation of symptoms frequency and others, such as throat pain, odynophagia, and halitosis [7]. **Table 2** illustrates the RSI questionnaire.

4.4 Reflux finding score

The Reflux Finding Score (RFS) was diagnosed to represent the physical manifestations of LPR evident during a fiberoptic laryngoscopy, which consists of eight items of the commonest laryngeal findings seen during LPR with a maximum score of 26. The mean RFS for LPR patients pretreatment was 11.5 with a significant trend of improvement to 6.1 at 6 months upon initiating treatment [22]. It is used as a tool for the standardization of findings among clinicians for assessment, treatment follow-up, and efficacy. A score of >7 is considered abnormal and diagnostic of LPR [22]. However, RFS does not represent extra laryngeal findings with a low inter-rater reliability [7, 25]. **Table 3** illustrates the RFS score assessment.

5. Diagnosis

The diagnosis of LPR relies on a good history and clinical examination (including laryngoscopy), which is supported by investigation. Upper esophageal pH probe monitoring is the gold standard in monitoring patients with LPR [26], which is difficult to reproduce, time-consuming, requires specialized skills, incurs further investigative costs, and may not be readily available at healthcare institutions in rural areas.

The combination of RSI which explores the symptomatology and RFS which explores the physical findings are useful with its simple-to-fill questions to aid the diagnosis of LPR. RSI and RFS used simultaneously have been shown to have statistically significant differences in pre and posttreatment LPR. LPR may be chronic and/or intermittent. The combination of RFS and RSI in addition to history and clinical examination helps in the early diagnosis of LPR and immediate commencement of treatment, which minimizes the LPR-associated complications and eases treatment follow-up.

6. Management

The management of LPR is multidisciplinary and there are three components of management that should be considered. Refer to **Figure 9** for the illustrated treatment algorithm of LPR.

6.1 Lifestyle and dietary change

Since lifestyle factors, such as stress and behavior, contribute to an increase in gastric acid production, therefore it should be identified and managed effectively. Primary care physicians play a significant role in identifying these issues and managing them [27]. Psychological stress is believed to activate the mast cells *via* the autonomic nervous system, which releases mast cells, resulting in an increase in the permeability of epithelial cells. Acid and pepsin stimulate intraepithelial nociceptors, stimulating pain and the sensation of heartburn [28]. Diet and obesity are also significant contributing factors. Foods that may worsen acid reflux such as spicy diet (either chili or spices) and oily diet, which includes fried food, alcohol, caffeine (tea or coffee), carbonated drinks, and milk, are common causative factors [27–29]. In overweight or obese patients, weight loss is pertinent to reduce intra-abdominal

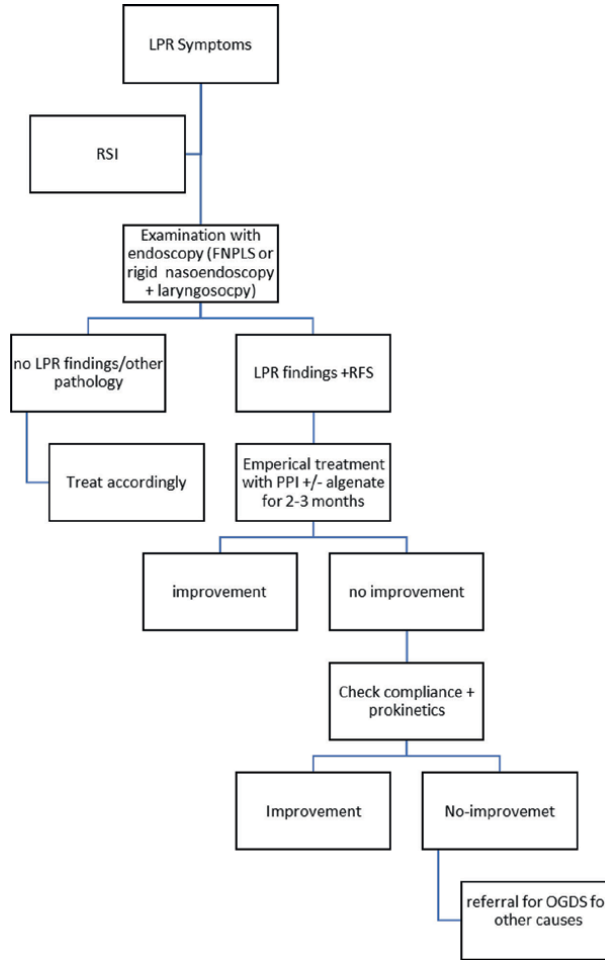

Figure 9.
Treatment algorithm for LPR.

pressure and improve esophageal sphincter function. Calorie restrictions and increasing activity levels can be managed by a dietitian and physiotherapist. Smoking, which is known to cause loosening of the lower gastroesophageal sphincter, should be stopped. A pharmacist may help with nicotine replacement therapy.

6.2 Pharmacotherapy

The mainstay of pharmacotherapy in managing acid reflux is the use of proton pump inhibitors (PPI). PPIs inhibit histamine-2–, gastrin-, and cholinergic pathways by irreversibly inhibiting the H + -K + ATPase proton pump on parietal cells, reducing the acidity and volume of gastric secretions. These, in turn reduce the availability of an acid medium for pepsin to function as an enzyme. PPIs should be consumed 30 to 60 minutes prior to meals, which allows for the highest concentration to inhibit gastric acid release during eating. Optimized administration of PPIs is twice daily doses of 40 mg of omeprazole or equivalent for 2 or 3 months [30]. These patients will need to be followed up with RSI and RFS scoring to assess improvements. It is believed that

GERD responds quicker to PPIs unlike LPR, which may improve in 3 months, but complete laryngeal symptomatic improvements may take up to 6 months [11].

There is a need to evaluate efficacy and diagnosis at 3 months and not hesitate to continue therapy and to ensure compliance with PPI therapy. Some may miss doses and not consume PPIs prior to meals. If there are improvements, this empirical therapy is indeed diagnostic and therapeutic to LPR [31]. If treatment is futile, there will be a need to revisit and revise the diagnosis. A referral to otorhinolaryngologist, gastroenterologist, or upper gastrointestinal surgeon for considerations of an OGDS and/or pH study shall there be no improvements at 2–3 months of optimum therapy. LPR symptoms are nonspecific, and these symptoms may hide another pathology within the esophagus and stomach. It is advisable to prevent prolonged dependency on PPIs, which are recently linked to chronic kidney disease. In Asian nations, H pylori is prevalent and should be ruled out as it contributes to acid reflux. The literature review has suggested a maximum therapy that involves addition of a H2 receptor antagonist at bedtime in addition to the two daily doses of PPIs before the morning and evening meals [11]. Prokinetic agents may be beneficial by speeding up gastric emptying and may be an option among patients with little benefit from optimum medical therapy. The literature is still unclear on its efficacy in LPR [32].

Pharmacotherapy for nonacid reflux involves alginates, which react with gastric acid to form a protective barrier to the upper intestinal mucosa, which is inexpensive and has an immediate onset of action by forming a barrier to protect the mucosa from further gastric acid irritation [11].

6.3 Surgery

Anti-reflux surgery is the step up and last resort of treatment if optimal pharmacotherapy has failed. For patients with significant hiatus hernia, laparoscopic fundoplication may be considered. A recent review of 844 patients found that laparoscopic fundoplication is beneficial with improvements in RSI among LPR patients resistant to pharmacotherapy [33]. Fundoplication has been effective in reducing heartburn, acid regurgitation, voice fatigue, chronic cough, choking, sore throat, and globus sensation. It was not very beneficial in alleviating throat clearing and adult-onset asthma [34].

7. Conclusion

LPR previously deemed a controversial topic in laryngology is now clearer with a better understanding of the pathogenesis. Diagnosis is made based on symptoms, and laryngoscopy aided with investigations and confirmed the response to treatment.

Author details

Hardip Singh Gendeh[1*] and Balwant Singh Gendeh[1,2]

1 Department of Otorhinolaryngology, Head and Neck Surgery, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia

2 Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

*Address all correspondence to: bsgendeh@gmail.com

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Section 4

Laryngeal Airway and Lesions

Chapter 4

Vocal Cord Paralysis

Shaili Priyamvada

Abstract

Vocal cord paralysis can be due to neurogenic cause, trauma due to surgery, or mechanical fixation of the cords. Diagnosis of the underlying cause leading to paralysis of the vocal cords is important. Most commonly, there is paralysis of recurrent laryngeal nerve. Treatment depends on the cause and whether the cord paralysis is unilateral or bilateral. Unilateral paralysis patients usually present with change in voice, regurgitation, and difficulty in swallowing. One-third of them they show spontaneous recovery, due to compensatory movement of opposite healthy vocal cord. Speech therapy is useful during initial conservative management period. In rest of the cases, vocal cord medialization procedures are performed. As for bilateral vocal cord paralysis which is troublesome entity, patients present with severe symptoms of respiratory distress, stridor, and aspiration. Voice is usually normal in bilateral paralysis cases but change in pitch, poor intensity, and voice fatigue are the complaints. The primary objective is to relieve patients' dyspnea. There are different treatment options available for bilateral vocal cord paralysis such as tracheostomy, arytenoidectomy, cordectomy, botulinum toxin injection, re-innervation procedures. All these procedures have been applied in with varying success. Unilateral cord paralysis is more common and has better prognostic outcomes as compared to bilateral vocal cord paralysis.

Keywords: vocal cord paralysis, change in voice, stridor, tracheostomy, arytenoidectomy

1. Introduction

Larynx plays role in phonation, respiration, airway protection, prevention of aspiration, and swallowing. The extrinsic muscles are associated with swallowing, while the prime function of intrinsic muscles is respiration and phonation.

Vocal cord refers to the immobility of vocal cord. It can be unilateral or bilateral. Both can be due to diseases affecting the vocal cord itself such as tumor or scarring; or due to paralysis of recurrent laryngeal nerve or superior laryngeal nerve.

The most common causes include laryngeal or extralaryngeal cancers, iatrogenic trauma during neck, thyroid gland, or chest surgery, and various neurogenic conditions (e.g., amyotrophic lateral sclerosis and closed head injury) [1–4].

Vocal cord paralysis is most commonly unilateral. The affected vocal cords do not adduct or abduct properly causing voice disorder. Along with that there might be difficulty in swallowing. As for bilateral paralysis, breathing difficulty, choking, and aspiration are there along with voice change. The incidence of the bilateral vocal cords paralysis comprises around one-third of all vocal cord paralysis cases [2].

It requires interprofessional team of otolaryngologists, radiologists, and speech therapists in the evaluation and management of vocal cord paralysis.

2. Positions of vocal cords

Five positions of vocal cords are described traditionally (**Table 1**; **Figure 1**). The position of the vocal cords may not correlate with the severity and site of the lesion and, thus, is not a reliable indicator. As re-innervation occurs the position of the vocal cord often changes.

Median position: Vocal cord is in midline position such as in phonation. It may occur in recurrent laryngeal nerve (RLN) paralysis.

Paramedian position: Vocal cord is 1.5 mm away from midline. It occurs in strong whisper in a healthy person. It may occur in RLN palsy.

Intermediate (cadaveric): This is the neutral position of vocal cords. Abduction and adduction occur from this point. Vocal cord lies 3.5 mm away from mildline. This occurs when there is combined paralysis of RLN and SLN.

Slight abduction: Vocal cord is 7 mm away from the midline. It occurs during quite respiration and paralysis of adductors.

Position of vocal cords	Location of the cord from midline	Healthy	Diseased
Median	Midline	Phonation	RLN paralysis
Paramedian	1.5 mm	Strong whisper	RLN paralysis
Intermediate(cadaveric)	3 mm, this is the neutral position of vocal cords.		Paralysis of both RLN & SLN
Gentle abduction	7 mm	Quite respiration	Paralysis of adductors
Full abduction	9 mm	Deep respiration	—

Table 1.
Position of vocal cords from midline in healthy and diseased individuals.

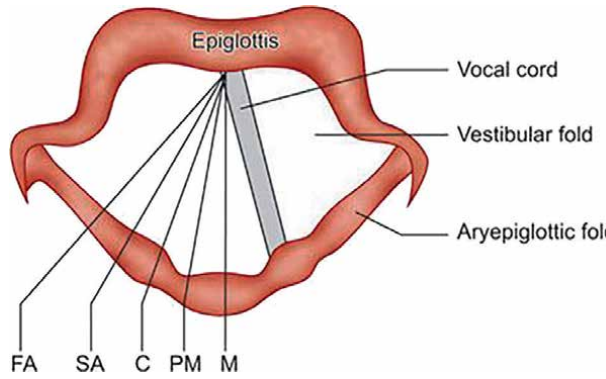

Figure 1.
Diagram showing different positions of vocal cords (FA—full abduction, SA—slight abduction, C—cadaveric, PM—paramedian, M—median).

Full abduction: Vocal cord in 9 mm away from midline such as in deep respiration.

3. Etiology of vocal cord paralysis

Causes of vocal cord paralysis include

1. Supranuclear-stroke, tumor, meningitis, or head injury. Diffuse emboli in cerebral cortex may cause sustained abduction(aphonia) or inappropriate adduction(inspiratory stridor).

2. Nuclear-lesions of Nucleus ambigus in medulla, usually associated with other lower cranial N. paralysis, stroke, tumors, motor neuron disease, poliomyelitis, syringobulbia.

3. High vagal lesions—Intracranial: Tumors of posterior fossa, Basal meningitis(tubercular).

    1. Jugular foramen (skull base): Fractures, nasopharyngeal cancer, Glomus tumor, skull base osteomyeltis.

    2. Parapharyngeal space: Penetrating injury, parapharyngeal tumor, metastatic nodes, lymphoma.

4. Low vagal lesions or RLN: Most common cause, refer **Table 2**.

Right	**Left**	**Both**
Neck trauma	1. Neck Accidental trauma	
Benign or malignant thyroid disease	Benign or malignant thyroid disease	
Thyroid surgery	Thyroid surgery	
Carcinoma cervical esophagus	Carcinoma cervical esophagus	Thyroid surgery
Cervical lymphadenopathy	Cervical lymphadenopathy	Carcinoma thyroid
Subclavian artery aneurysm	2. Mediastinum	Carcinoma cervical esophagus
Carcinoma apex right lung	Bronchogenic carcinoma	Cervical lymphadenopathy
Tuberculosis of cervical pleura	Carcinoma thoracic esophagus	
Idiopathic	Aortic aneurysm	
	Mediastinal lymphadenopathy	
	Enlarged left auricle	
	Intrathoracic surgery	
	Idiopathic	

Table 2.
Causes of recurrent laryngeal nerve paralysis (low vagal trunk or RLN).

5. Systemic causes: Diabetes mellitus, diphtheria, typhoid, lead poisoning, amyotrophic lateral sclerosis (ALS), Guillain-Barre syndrome(GBS).

6. Idiopathic—In around 30% of cases.

4. Unilateral vocal cord paralysis

4.1 Epidemiology

Studies on comparison of patient demographics show no statistically significant difference in age, gender, or duration of symptoms. About one-third of UVCP cases are neoplastic in origin, one-third are post traumatic and one-third are idiopathic. Viral neuronitis probably accounts for most idiopathic cases. Paralysis of the left vocal cord is reported to be 1.4–2.5 times more than right [5].

4.2 Pathophysiology

RLN damage is the most common cause of vocal cord paralysis. Combined paralysis of RLN and SLN is also possible and is seen post-thyroidectomy surgeries due to iatrogenic trauma.

To understand the pathophysiology of vocal cord paralysis, it is of importance to know the origin and course of vagus nerve and its branches as they give rise to laryngeal sensory and motor supply.

Vagus nerve has two nuclei—nucleus ambiguous and dorsal nucleus of vagus. Nucleus ambiguous is situated in medulla and gives origin to motor efferent fibers to soft palate, pharynx, and larynx. Dorsal nucleus of vagus is an autonomic nucleus, which gives general efferent visceral fibers that supply smooth muscles and glands of trachea and bronchi, heart, and abdominal viscera.

The superior laryngeal nerve arises from inferior ganglion of vagus and descends behind internal carotid artery, and at the level of greater cornua of hyoid, it divides into internal and external branches. The internal branch travels medially along superior laryngeal branch of superior thyroid artery and pierces the thyrohyoid membrane about 1 cm anterior to greater cornu and about 1 cm above ala of thyroid cartilage. The nerve then runs submucosally in the lateral wall of pyriform fossa. It provides sensory innervation to the mucosa above the true vocal cords. The external branch runs along the posterior aspect of superior thyroid artery and proceeds inferiorly along oblique line of thyroid. As it reaches inferior constrictor muscle, it sends a branch and then passes deep to sternothyroid muscle to reach the cricothyroid muscle. It innervates the cricothyroid muscle (essential in changing the pitch of the voice). Isolated superior laryngeal nerve lesions are rare and it is usually part of combined paralysis. It results in loss of sensation above the level of true vocal cords and a husky voice.

On the right side, RLN arises from vagus in front of subclavian artery in lower part of neck, and it traversus below the subclavian artery after emerging from vagus nerve. RLN is derived from sixth arch and is displaced by arteries of previous arch, which necessitates change in direction and course of recurrent laryngeal nerve. The right recurrent laryngeal nerve stays lateral to the trachea-esophageal groove in the fat plane and comes closure to the groove as it crosses inferior thyroid artery. The left RLN has longer course and from its origin at the anterior surface of arch of aorta to the interspace

between origin of left common carotid artery and subclavian artery. The nerve loops around arch of aorta distal to ligamentum arteriosum and then enters the neck, and lies deeper in the trachea-esophageal groove. Rest of the course is in similar on both sides, as RLN reaches the suspensory ligament of thyroid gland and lies on either medial or lateral from within. Then, it divides to supply the intrinsic muscles of larynx. Left RLN is more prone for injury as it has a longer course and injury most commonly occurs in the region of trachea-esophageal groove during thyroid or any other neck surgery.

There are two theories to explain the position of vocal cord in cases of cord paralysis. Semon's law states that in the sequence of position of the vocal cords in slowly progressive organic central lesions, motor nerve fibers supplying the abductors of vocal cords become involved much earlier than adductors. Wegner and Grossman hypothesis explains the median and paramedian position of cords after RLN palsy, on the basis that cricothyroid muscle that receives supply from superior laryngeal nerve takes over & it has adductor and tensor function.

4.3 History and physical examination

Patients with unilateral cord paralysis present with a sudden onset of change in voice, that is, dysphonia and/or transient aphonia. In addition to dysphonia, a significant proportion of patients present with swallowing difficulties, weak cough reflex, and regurgitation. Poor exercise tolerance with shortness of breath on minimal exertion is observed in many patients with UVCP in spite of normal lung function.

It is important to obtain elaborate history including the symptoms and signs pertaining to head and neck cancer. History of pain during swallowing, hemoptysis, neck nodes, referred ear pain, and significant weight loss should be asked. Past medical history including heart or lung disease, smoking, tobacco chewing, and alcohol consumption status are all important indicators of potential malignant disease. Clinical evaluation of the patient should include a complete otolaryngological examination, with particular attention to inspection and palpation of the neck. Flexible nasal endoscopy of the oropharynx and glottis helps forming the diagnosis. Assessment of voice quality can be graded with GRBAS scale (Grade, Roughness, Breathlessness, Aesthenia, Strain) [6], which has frequently shown the voice to be worse in such patients.

4.4 Evaluation

4.4.1 Flexible videolaryngoscopy

Flexible laryngoscopy of the glottis is the most useful method of evaluating appearance and movement of vocal cords. It is easily performed in the outpatient setting and can be combined with videostroboscopy to obtain a detailed overview of vocal cord movements (**Figure 2**).

4.4.2 Videostroboscopy

Videostrobscopy uses the same equipment as videolaryngoscopy combined with a microphone and flashing strobe light. During speech production, our vocal cords move at a very high speed, too fast to be perceived by naked human eyes. Stroboscopy is used to "slow down" the movement to study the detailed vocal cord movements such as amplitude, mucosal wave, vibratory pattern. It is a gold standard test in cases of voice disorders (**Figure 3**).

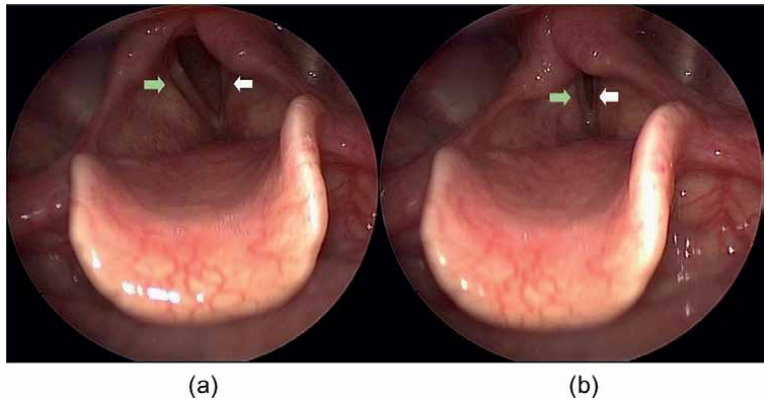

Figure 2.
Videolaryngoscopy showing left vocal cord paralysis post left hemithyroidectomy (a)abduction (b) adduction.

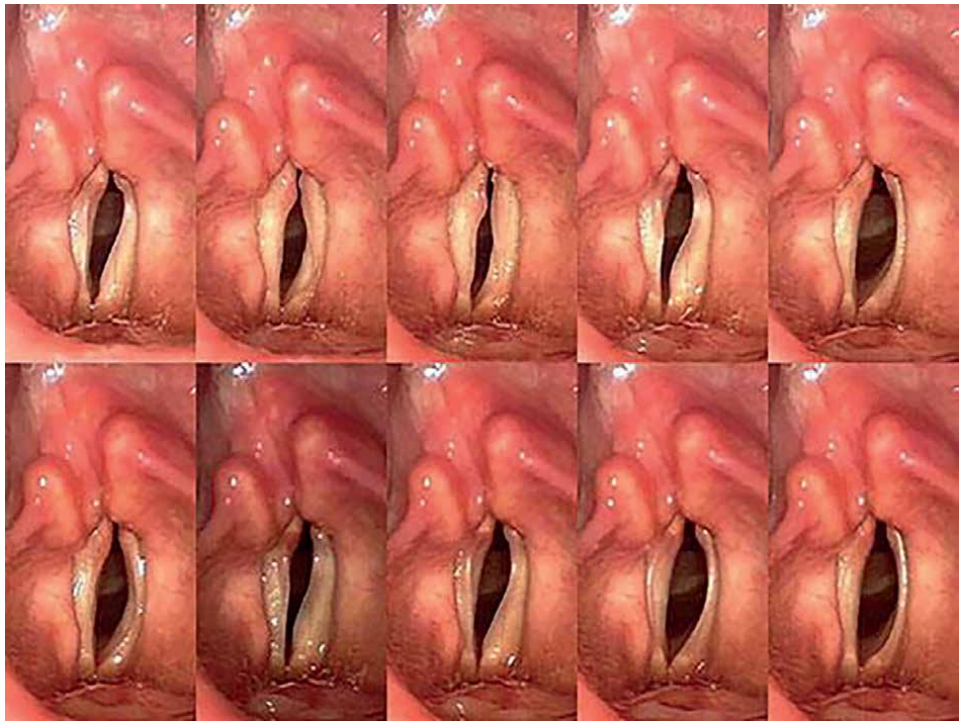

Figure 3.
Videostroboscopy pictures showing right vocal cord paralysis.

4.4.3 Imaging

A *chest X-ray* can be useful in cases of mediastinal or lung lesions and to read features of aspiration pneumonia. *CT scanning* is the most favored investigation. CT from skull base to diaphragm is adviceable in order to study the complete course of RLN. MRI can be used an alternative to CT scan when exposure to ionizing radiation is a concern but it has high false-positive rates.

Neck and laryngeal ultrasound can be used to assess vocal cord movement and investigate surrounding pathologies. However, ultrasound does not yield the same anatomical definition as CT requires an experienced ultrasonographer and is less reliable in obese patients.

4.4.4 Lab tests

Routine serological testing only aids in the diagnosis of a particular etiology. There is no strong evidence of them in helping form a diagnosis. Serum tests can be used in suspected inflammatory or infectious UVCP, with common tests including rheumatoid factor, antinuclear antibodies, serum ACE, lyme titer, and erythrocyte sedimentation rate (ESR).

4.4.5 Laryngeal electromyography

Laryngeal electromyography can be used as a prognostic tool. It is an office-based procedure. A percutaneous EMG needle is inserted through the anterior part of neck to the muscles of the larynx and their electrophysiological evaluation is done. Although growing in popularity, the test is not widely available.

4.5 Treatment/management

Patients with UVCP are initially treated with speech therapy. A "watchful waiting" period of 6 to 9 months is observed for spontaneous motion recovery by the opposite healthy vocal cord, as there is no definitive guidelines on how long a clinician should wait before surgical intervention.

The aim of surgery in cases of unilateral cord paralysis is cord medialization. The different surgical options are as follows:

Intracordal injection or injection thyroplasty—this involves injection of a substance to the affected vocal cord, moving it medially to make better contact with the opposite vocal cord. Different materials have been used in injection thyroplasty, for example, autologous fat, teflon, collagen, gelfoams, calcium hydroxy-apatite, methyl-cellulose, and hyaluronic acid; however, no high-quality evidence exists confirming the ideal material [7]. Teflon has previously been used, but this has fallen out of favor due to the formation of granulomas.

Type 1 Isshiki thyroplasty is a medialization procedure wherein a window is cut into the thyroid cartilage, and the vocal cord moved medially by the use of an implant such as silastic prosthesis. Like injection thyroplasty, there are numerous implant materials available. Arytenoid rotation procedures such as adduction and arytenopexy can be performed concurrently, and voice outcomes are reported to be good at 1 and 3 years post-operatively [8].

Dynamic procedures like nerve-muscle pedicle transfer with superior belly of omohyoid muscle along with its nerve(ansa hypoglossi) and vessels is implanted into thyroarytenoid muscle. Ansa cervicalis-recurrent laryngeal nerve anastomosis has also been used with good results on voice outcomes.

Type 1 Isshiki thyroplasty has a greater long-term benefit over injection techniques, and there is a growing body of evidence that long-acting injectable materials have comparable longitudinal outcomes [9]. Surgical intervention should be considered after a trial of conservative management, with the technique used based on surgeon experience and patient preference.

4.6 Prognosis

Around one-third of patients of UVCP will experience motion recovery, due to the compensatory action of the opposite vocal cord [10]. Laryngeal electromyography is an useful tool to track prognosis in patients with persistent dysphonia [11].

4.7 Complications

The adverse effect on voice and swallowing can have a significant detrimental impact on the patient's quality of life. Incomplete closure of the glottis can also lead to a risk of aspiration, and despite being rare, this can lead to life-threatening aspiration pneumonia. In particular, patients who rely on their voice for a living (teachers, singers, secretaries) may suffer significant psychological and financial difficulty as a result of UVCP.

4.8 Enhancing healthcare team outcomes

The interprofessional team approach is better in diagnosing and managing cases of UVCP. Otolaryngologists can diagnose it with elaborate history, clinical examination, and flexible video laryngoscopy. Radiologists can aid in diagnosis through the study of the course of nerve involved or mediastinal lesion through CT /MRI imaging. Management can be done with speech therapy with the support of speech and language therapists and surgical treatment for those patients by otolaryngologists who do not respond to initial therapy.

5. Bilateral vocal cord paralysis

The most common presentation of bilateral vocal cord paralysis is stridor [12]. These patients typically present with respiratory distress. In addition to considerable airway obstruction, bilateral vocal cord paralysis presents with symptoms common in unilateral vocal cord immobility such as ineffective cough, aspiration, recurrent pneumonia, reactive airway disease, and feeding difficulties [13, 14]. Voice and cry may be fairly normal in children with bilateral vocal cord paralysis [15].

5.1 Epidemiology

As bilateral vocal cord paralysis occurs most commonly after iatrogenic trauma to recurrent laryngeal nerve, there is history of recent thyroid surgery in these patients. The incidence of the bilateral vocal cords paralysis comprises around one-third of all vocal cord paralysis cases. Bilateral cord paralysis is slightly more common in females, and it is attributed to the fact that thyroid diseases are more common in them as compared to males. Idiopathic bilateral paralysis cases show no gender preponderance and incidence is equal in both males and females.

5.2 Pathophysiology

RLN damage is the most common cause of bilateral vocal cord paralysis. Combined paralysis of RLN and SLN is also possible and is seen post-thyroidectomy surgeries due to iatrogenic trauma.

Bilateral vocal cord paralysis can be caused by injury to the vagus nerve near its origin or anywhere along its course or injury to its branches RLN and SLN through neck, thorax, and abdomen. Injury to the RLN is most common, classically leaving the vocal cords in a median position in case of bilateral vocal cord paralysis. Injury to the SLN will lower the pitch of the voice and can lead to a bowing deformity of the vocal cords due to a loss of tone from the dennervated cricothyroid muscles. A high vagal injury can leave the cord in a nearly fully abducted position.

5.3 History and physical examination

A bilateral vocal cord paralysis patient most commonly presents with breathing difficulties such as stridor, increased work of breathing, and aspiration. It can be life-threatening and immediate measures that have to be taken to secure the airway. Voice in bilateral paralysis is usually of good quality but of limited intensity, changed pitch, and with voice fatigue. Any recent history of URI, any neck or mediastinal surgery or trauma, malignancy, radiation therapy, and a thorough past medical history should be obtained. A thorough physical examination is done, with an emphasis on the head and neck and lung examination.

Clinical diagnosis can be made based on flexible fiber-optic laryngoscopy, where the vocal cord position can be noted and are observed to be immobile. If the diagnosis is still uncertain, video stroboscopy and bronchoscopy can provide additional information about motion wave of the vocal cord vibrations and rule out subglottic and tracheal pathology, such as subglottic stenosis or tracheomalacia.

5.4 Evaluation

The investigations that aid in diagnosis are as follows:

Flexible videolaryngoscopy: It is essential part of the initial physical examination and is performed with the patient awake in the office to assess vocal cord movement. Direct laryngoscopy and bronchoscopy are reserved for the patients when there is any doubt about the diagnosis and patients with lung pathology, to visualize the lower airway. This procedure also allows palpation of the arytenoid joints to rule out fixation of vocal cords (**Figure 4**).

Laryngeal electromyography: This is an office procedure performed to determine the innervation status of the laryngeal muscles after a neurogenic injury. It is also useful as a prognostic tool during the recovery period.

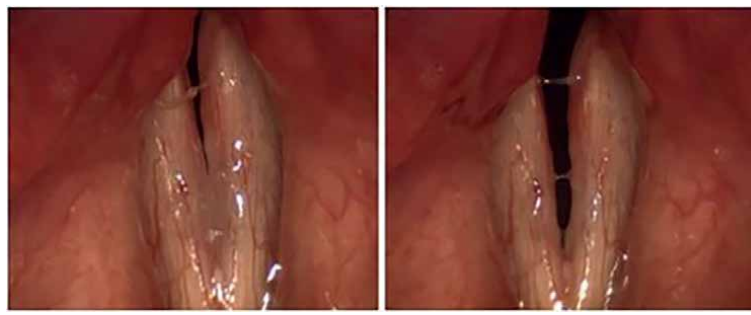

Figure 4.
Videolaryngoscopy pictures showing bilateral vocal cord paralysis.

Imaging of the recurrent laryngeal nerve CT is the most commonly employed investigation, though MRI can also be used. The area from brainstem to mediastinum is imaged to study the origin and entire course of vagus nerve and its branches RLN and SLN and detect pathology.

Lab tests: Blood investigations depend upon history and overall medical scenario of the patient. Antineutrophil cytoplasmic antibody test, thyroid function tests, tubercular skin tests, uric acid levels, rheumatoid factor test, serum K+, Ca+, Na+, antinuclear antibody tests, and erythrocyte sedimentation rate can all be considered.

5.5 Treatment

In bilateral cord paralysis, patient adequate airway must be re-established. Common surgical options for management include tracheostomy, arytenoidectomy, and cordotomy. Laryngeal re-innervation techniques and botulinum toxin (Botox) injections into the vocal fold adductors have also been used with varying success rates. More recently, there has been research on neuromodulation, laryngeal pacing, gene therapy, and stem cell therapy. These newer approaches have the potential to recover the vocal cord movement without any anatomical destruction. However, clinical data are limited for these new treatment options, and more interventional studies are needed. These areas of research are expected to provide dramatic improvements in the treatment of bilateral cord paralysis in future.

Tracheostomy is the most common procedure performed in patients with bilateral vocal cord to establish a secure airway. It is potentially reversible without long-term sequelae. Although tracheostomy remains the standard in bilateral cord paralysis cases, it is associated with reduced quality of life, chronic care burden, cost, psychosocial impairment, and increased mortality. Endoscopic techniques have been shown to be more cost effective as compared to tracheostomy in the management of permanent bilateral vocal cord paralysis [16]. Although several alternative procedures have been developed to manage bilateral vocal cord paralysis, they all have the ability to produce permanent changes of the larynx that may predispose patients to lifelong aspiration and dysphonia postoperatively. *Arytenoidectomy* is an irreversible procedure where there is an endoscopic removal of the arytenoid cartilage to expand the glottic chink transversely, for adequate airway. It is either performed on its own or in combination with vocal fold resection, referred to as arytenoid cordectomy. In current scenario, it is performed using *CO2 laser* or KTP-532 laser, which aids in precision, achieving better hemostasis and reducing postoperative edema. Arytenoidectomy has positive results in terms of augmenting ventilation but some patients may experience worsening dyspnea after the procedure, which can be permanent. Arytenoidectomy can also lead to scarring and granuloma formation. In such cases, multiple surgical revisions are needed. Endoscopic plasma *coblator* can also be used to perform arytenoidectomy. *Cordotomy* is another endoscopic surgical procedure to enlarge the glottic chink to attain adequate airway. An incision is made in the vocal cord, ligament, and the thyroarytenoid muscle posteriorly at the attachment to the arytenoid. Revision cordotomy can be required in up to 30% of patients secondary to reduced glottic diameter from scarring or granulation tissue formation [17]. The most common complication associated with cordotomy was altered voice quality due to vocal fold damage [18]. Laser endoscopic cordotomy is preferred now, as compared to an arytenoidectomy, in vocal cord paralysis cases as it is less invasive and reduces the incidence of aspiration. Also, overall voice outcomes are also better than arytenoidectomy.

Botulinum toxin injection to adductor muscles provides transient improvement in symptoms for approximately three to 6 months at a time, requiring repeated injections for longer-lasting relief.

Reinnervation techniques are technically challenging and require experienced surgeons in its use for the procedure to be a success. The goal here is to establish vocal cord abduction through the restoration of the activity of the posterior cricoarytenoid (PCA) muscle. While it enables the return of spontaneous vocal cord abduction, it does not affect adduction. Gene therapy and stem cell therapy are in preclinical stage but hold promising for treatment in future.

5.6 Prognosis

In adults, spontaneous recovery of idiopathic vocal cord paralysis can occur as early as 12 months following the onset. It is expected in 55% of patients, but full recovery can be very protracted. The prognosis for complete spontaneous recovery is far worse in bilateral vocal cord paralysis than unilateral. Recovery depends upon the underlying etiology.

5.7 Complications

Bilateral cord paralysis can lead to the following complications: Stridor, airway obstruction, dyspnea, poor cough reflex, aspiration, bronchopneumonia due to aspiration, difficulty in swallowing, feeding difficulties, and failure to thrive in children & voice fatigue. In addition to this, in the long-run arytenoid granuloma formation and chondritis may occur.

5.8 Enhancing healthcare team outcomes

Bilateral vocal cord paralysis is a challenging and troublesome entity. Tracheostomy, cordotomy, and arytenoidectomy all have been applied with positive outcomes in bilateral cord paralysis cases. Management should be individualized based on the patient's clinical presentation and the surgeon's expertise.

6. Paralyzed versus fixed cord

Vocal cord fixation is immobility of vocal cords due to scarring or due to mass effect, involvement of muscles, and joints or the nerve as in case of malignancy. Cord fixation can also be due to rheumatoid arthritis. There may be obvious swelling around cricoarytenoid joint, cord is immobile and fixed, its position does not correspond to any of the described anatomical positions of vocal cords, and aryepiglottic folds are normal. There is no change in position on applying pressure passively on arytenoids, which is in contrast to vocal cord paralysis. Also, in cases of fixation there is absence of any neurological symptoms and signs. In cases of vocal cord paralysis, aryepiglottic folds are paralyzed and pushed aside, cord is fixed to median or paramedian position, but there is no fixation of the joint and it is mobile on manipulating passively. Also, cord paralysis is purely a neurological condition in contrast to cord fixation.

7. Laryngeal paralysis in children

Vocal cord paralysis presents more commonly as stridor in neonates and children. It can be unilateral or bilateral in children, unilateral being more common. Vocal cord paralysis is the second most common cause of stridor in pediatric population following laryngomalacia and accounts for 10% of all congenital anomalies of larynx. Murty et al. estimate the incidence of bilateral vocal cord paralysis to be 0.75 cases per million births per year. Congenital vocal cord paralysis should be part of the differential diagnosis for an infant with respiratory distress. In up to 48–62% of neonates and children with bilateral vocal cord paralysis, spontaneous recovery of vocal cord function can occur, but the prognosis rests with the overall health of the child and any concomitant medical problems [19].

7.1 Etiology

Birth trauma due to vertex or breech delivery and the use of forceps can also lead to RLN injury, though less commonly a bilateral injury [20]. In infants, cardiovascular surgery, including patent ductus arteriosus ligation, and repair of a tracheoesophageal fistula are the common causes of bilateral vocal cord paralysis [21]. **Table 3** summarizes causes of congenital vocal cord paralysis.

7.2 History and physical examination

A detailed family and perinatal histories, including prolonged or protracted or forceps-assisted delivery, concurrent congenital conditions and length of any NICU stay, should be inquired. Presenting symptoms in children include stridor, a weak cry, feeding difficulties, failure to thrive, and aspiration. Neonates and children with bilateral cord paralysis are likely to exhibit severe manifestation such as cyanosis and apnea. Bilateral cases usually have good voice because vocal cords are in median or paramedian position with abductor paralysis but can have marked inspiratory stridor and accessory muscles of respiration working.

Diagnosis can be made by awake fiber-optic laryngoscopy and careful evaluation of the larynx by an experienced pediatric otolaryngologist. Laryngomalacia should be considered as differential diagnosis and ruled out during laryngoscopy, which is far more common than bilateral vocal cord paralysis but can have similar presenting symptoms.

If the diagnosis is still uncertain, direct laryngoscopy and bronchoscopy can be performed under general anesthesia. This is done with the patient spontaneously

Unilateral	**Bilateral**
More common	Causes
Causes	Hydrocephalus
Birth trauma	Arnold-chiari malformation
Congenital anomaly of	Intracerebral hemmorrhage
Great vessels of heart	Myelomeningocele
	Cerebral agenesis

Table 3.
Causes of congenital vocal cord paralysis.

breathing so the motion of the vocal cords can be assessed intraoperatively. This also allows lower airway examination to rule out concurrent or alternate pathology such as subglottic stenosis and trachea- or bronchomalacia.

7.3 Treatment

Before surgical treatment is considered, parents are advised to position the child so that he or she is sitting up and to thicken the food in order to manage feeding difficulties and milk regurgitation. If gastroesophageal reflux is suspected, then this should also be treated. In addition, all children with vocal cord paralysis should be seen by a speech pathologist. Greater than 50% of children will undergo spontaneous symptom resolution in the first 12 months of life, though the prognosis is much more guarded for bilateral vocal cord paralysis cases when compared with unilateral [22].

There are no definite guidelines on when to perform surgery and the decision is difficult since in children spontaneous recovery may occur anytime over the years. It should be guided according to the individual case. In general, for cases of bilateral palsy destructive procedures such as cordotomy or arytenoidectomy are advised to be deferred till adolescence.

Tracheostomy is needed and should be performed to improve the airway in bilateral vord paralysis cases, even if spontaneous recovery is expected. Patient can be decanulated once vocal cord recovery occurs.

8. Conclusion

An integrated diagnostic and treatment program is necessary for patients with vocal cord paralysis. Otolaryngologists, speech therapist, and radiologists all play important role in evaluation and management. Treatment strategies should be individualized based on the patient's clinical presentation and the surgeon's expertise.

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Conflict of interest

The author declares no conflict of interest.

Abbreviations

RLN	recurrent laryngeal nerve
SLN	superior laryngeal nerve
UVCP	unilateral vocal cord paralysis
CT	computer tomographic imaging

MRI	magnetic resonance imaging
EMG	electromyography
ALS	amyotropic lateral sclerosis
GBS	Guillain-Barre syndrome
GRBAS scale	Grade, Roughness, Breathlessness, Aesthenia, Strain

Author details

Shaili Priyamvada
Department of Otolaryngology, Rama Medical College, Hospital and Research Centre, Ghaziabad, India

*Address all correspondence to: dr.shaili.priyamvada1@gmail.com

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Chapter 5

Laryngeal Leukoplakia: A Focus on Histology

Giuseppe Leoncini

Abstract

Leukoplakia is a clinical term referring to a whitish plaque on the mucosal surfaces that cannot be scraped off. Otolaryngologists daily have to face such findings in both the oral cavity and the larynx. In the latter, several pathological conditions ranging from reactive to neoplastic lesions can underlie leukoplakia. Hence, a proper understanding of the histological spectrum of laryngeal diseases sharing leukoplakia as their main clinical presentation plays a critical role in the clinical management of patients. In that setting, the histological assessment of laryngeal dysplasia is known to have represented a matter of disagreement mostly about grading, and several grading systems have been proposed over time. Nonetheless, the histologic assessment of laryngeal leukoplakia is a mandatory requirement in clinical planning, leading to a proper treatment choice.

Keywords: leukoplakia, dysplasia, larynx, grading, differential diagnosis

1. Introduction

Laryngeal leukoplakia (LL) is a clinical term referring to the presence of a whitish plaque on mucosal membranes that cannot be scraped off [1]. Leukoplakia is a descriptive term having not a single histological counterpart but, on the contrary, a broad spectrum of pathological pictures, ranging from benign (reactive-inflammatory) lesions to dysplastic and neoplastic conditions. Establishing a proper diagnosis represents a unique challenge since the optimal clinical management depends on the identification of the reactive or dysplastic nature of that lesion. LL can be found at any laryngeal site, mostly onto the true vocal folds. Regardless of the clinical presentation, LL should be histopathologically examined to rule out both dysplasia and invasive carcinoma, which should be properly treated. Further complexity in managing LL relies on the frequent location along the vibratory side of the vocal folds, where scarring could produce functional consequences and voice quality impairment. Mucosal biopsies performed with flexible laryngoscope represent to date the most widely used diagnostic technique to obtain an earlier diagnosis. Early detection is the strongest prognostic factor affecting the patients' survival. However, the biopsy technique has some limitations, as mucosal sampling could underestimate the severity of the lesion first because of the poor depth of biopsy, then because of the histological heterogeneity of broader lesions [2, 3].

2. Histopathological assessment

2.1 Vocal folds' normal anatomy and histology

The true vocal folds are laryngeal structures consisting of both vocalis muscle and vocal ligament, covered by stratified squamous epithelium. The free edge is formed by the vocal ligament and its epithelial lining, representing the mobile top of the vocal folds and contributing to phonation. The vocal ligament is in continuity with the cricovocal (cricothyroid) ligament, extending from the thyroid cartilage to the vocal process of the arytenoid cartilages. The vocalis muscle lies laterally to the vocal ligament, extending from the vocal process of the arytenoids to the vocal ligament [4]. The true vocal folds are lined by nonkeratinized stratified squamous epithelium, as seen in the superficial rim of the ary-epiglottic folds, in the anterior epiglottic surface (**Figure 1**). In contrast, ventricle, ventricular folds, saccule, and subglottis are covered by ciliated columnar epithelium, with scattered goblet cells. Seromucinous glands can be found in small clusters within the loose stroma of the false vocal fold, whereas they are scattered in the lamina propria of ventricle, saccule, posterior epiglottic surface, subglottis. Seromucinous glands are usually scanty or absent in the true vocal folds [5]. The false vocal fold has no contractile structures, is covered by respiratory-type epithelium, and represents the upper limit of the ventricle, whereas the true vocal fold is the lower limit.

2.2 Histopathology

LL is an *umbrella clinical term* including several histological conditions. *Squamous cell hyperplasia* (or *keratosis*) is qualified by the thickening of a pre-existing squamous epithelium, usually involving basal and prickle cells. It can encompass the presence of conspicuous keratin layer, composed of a nuclear keratin scales (*orthokeratosis*) or by squamous cells with picnotic nuclei and dense cytoplasm (*parakerathosis*). A preserved cellular differentiation, based on both normal nuclear-to-cytoplasmic ratio and base-to-top epithelial maturation, qualifies epithelial hyperplasia excluding dysplasia. Squamous cell hyperplasia can show exuberant features, represented by prominent squamous tongues

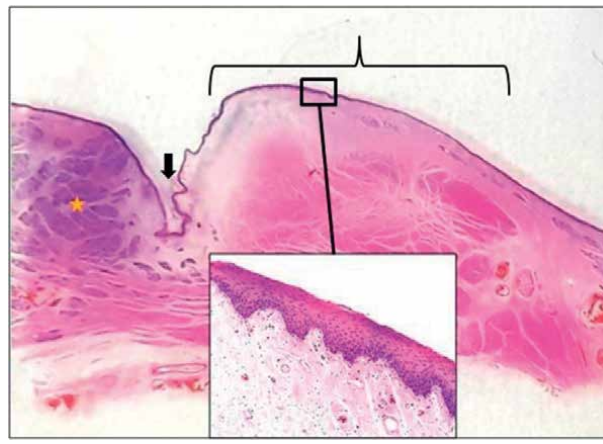

Figure 1.
Trans-sectional cut including both true and false (yellow mark) vocal folds. Arrow points to the laryngeal ventricle (hematoxylin–eosin, x2,5 magnification). Note that the true vocal fold's mucosa is covered by stratified squamous epithelium (insert, hematoxylin–eosin, x10 magnification).

simulating an infiltrative growth into the underlying stroma, thus mimicking well-differentiated squamous carcinoma. Such lesion is referred to as *pseudo-epitheliomatous hyperplasia*, a reactive lesion that can associate with chronic conditions. Squamous cell hyperplasia should be distinguished by *squamous metaplasia*, referring to the replacement of the ciliated respiratory-type epithelium by stratified squamous epithelium. It is a reactive phenomenon involving, by definition, those anatomical sites covered by non-squamous epithelium and can extend to the sero-mucinous glands. The term *diskeratosis* is sometimes used - but not widely accepted - to describe a focal abnormal maturation in the squamous lining, involving one or few cells displaying abnormal keratinization. It belongs to the spectrum of reactive squamous lesions.

3. Laryngeal leukoplakia in nonneoplastic diseases

The main histological feature of LL is represented by the epithelial thickening (hyperplasia) with preserved epithelial maturation or cellular atypia. Conversely, the presence of abnormal epithelial maturation and cellular atypia should raise suspicion for dysplasia. Despite the clinical setting of LL, dysplasia should be always suspected and ruled out through a proper histological assessment of mucosal specimens. In this regard, biopsy interpretation represents a critical part of the patient's management.

3.1 Phonotrauma

LL represents the main clinical presentation of laryngeal dysplasia and carcinoma. Nonetheless, it can also be detected in inflammatory disease of the upper airways. The so-called *phonotrauma* is a common clinical condition deriving from the improper use of phonation and characterized by an altered quality of voice, manifesting with hoarseness, rough or scratchy voice, and vocal fatigue. During phonation, the vocal folds' vibration represents a major physical threat. Indeed, both the magnitude and directions of the vocal folds' collision determine mechanical stress and subsequently an injury. The stratified squamous epithelium represents the outermost layer lining the vocal folds, supported by loose stroma and muscle. In some instances, the epithelial damage can extend down to the basal cell layer. Because of impact, stretching, and shearing forces, both the epithelial and the underlying loose connective layers could be affected, the latter being characterized by vascular and fibrotic changes, leading to the vocal folds' tendency to prolapse toward polyps' formation. In the setting of phonotrauma, epithelial reactive alterations could be seen, with or without stromal changes. A structural compromission of the vocal folds' epithelial barrier after acute phonotrauma has been reported by some Authors [6–10]. At histology, the epithelial lining is usually thicker than normal, showing several degrees of dyskeratosis, ranging from apoptotic-like epithelial changes to cytoplasmic clearing and ballooning. Epithelial maturation is preserved, sometimes associated with mild orthokeratosis. Inflammatory cells are usually absent or scanty. At fiberoptic examination, lesions usually appear as a slightly raised white plaque with ill-defined margins. Stromal changes could associate, giving rise to a bulging area or nodular/polypoid lesions.

3.2 Chronic laryngitis

Laryngeal inflammation for at least 3-weeks-long is usually referred to as *chronic laryngitis*. It can result from several etiologies, ranging from infectious (bacterial, viral,

fungal) to chronic inflammatory (tobacco smoke-related and reflux-related) conditions. Both symptoms and laryngoscopy are usually nonspecific. The great majority of bacterial laryngitis has an acute clinical course, characterized by prominent exudates and crusting. Chronic laryngitis should be suspected in those patients with prolonged impairment of the quality of voice. Viral infection is mainly due to Herpes Simplex Virus, which usually causes acute laryngitis, whereas chronic infection is rare. It is characterized by laryngeal edema, mucosal ulceration, and exudates. Fungal infections could run asymptomatic in immune-competent hosts. Such infections are seldom found in the larynx, being more common in the oral cavity. Immune compromission, drugs, previous radiotherapy, intubation, and neoplasms are common predisposing conditions. The most complained symptoms are hoarseness, cough, and local pain. Histology is not routinely obtained in inflammatory laryngeal diseases. When biopsy is performed, the histological picture is characterized by epithelial hyperplasia, ortho- or parakeratosis, and mixed inflammatory cells. The detection of PAS-D positive rod-like structures on the mucosal surface is diagnostic for fungal infection (**Figure 2**). Particularly, they could be superficially located, with scanty intra-epithelial neutrophil infiltration. Pseudo-epitheliomatous features can be observed. Patients suffering from Gastro-Esophageal Reflux Disease (GERD) frequently complain about laryngeal symptoms over time, such as hoarseness and cough. During the past years, the role of gastric acid reflux in determining laryngeal inflammation has been debated. Though chronic acid gastric reflux can promote laryngo-pharyngeal inflammation, only a minority of patients with clinically diagnosed reflux laryngitis shows pharyngeal reflux, with a similar prevalence in both healthy and reflux-laryngitis patients. Nonetheless, occult laryngeal pathology is known to be common in the adult population and laryngo-pharyngeal reflux has been reported as one of the most prevalent conditions [11, 12]. Mirroring the histologic picture seen at the gastro-esophageal junction, the vocal folds' mucosa is characterized by a variable degree of epithelial thickening, basal intercellular space dilation (spongiosis), and few intra-epithelial lymphocytes and granulocytes. Mild sub-epithelial edema is not uncommon. Current smokers have a

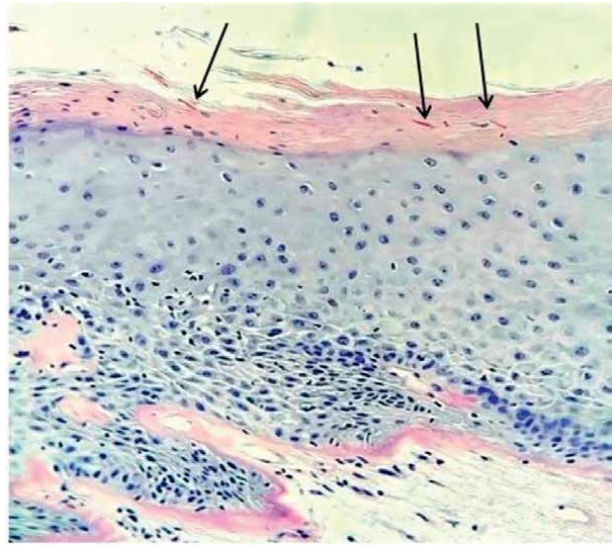

Figure 2.
Mucosal sample of true vocal fold in patient with laryngeal fungal infection. Note the rod-like structures (arrows) over the superficial epithelium (periodic acid-Schiff -diastase [PAS-D] x10 magnification).

higher risk to develop LL compared to never-smoker patients [13], with or without dysplasia. Chronic laryngitis can frequently underlie LL in smokers. In such circumstances, vocal folds' inflammation is characterized by mild-to-moderate subepithelial infiltration composed of lymphocytes, plasma cells, and histiocytes. Squamous cell hyperplasia and variable ortho- and para-keratosis are not uncommon findings. Dysplastic foci or invasive squamous cell carcinoma could associate.

3.3 Laryngeal involvement in systemic non neoplastic diseases

Larynx can be rarely involved in systemic diseases, such as autoimmune diseases that could mimic chronic laryngitis. Laryngeal lichen planus (LP) is a rare - and probably under-recognized - autoimmune disease affecting both skin and mucosal membranes. Although mucosal LP is more frequent in the oral cavity, where it should be distinguished from pemphigoid of the mucosal membranes, laryngeal involvement has been reported as well. As in chronic laryngitis, laryngeal LP harbors sub-epithelial inflammation, squamous hyperplasia, and superficial ortho- and para-keratosis without dysplasia but, in contrast, laryngeal LP usually presents at least focally, with a sub-epithelial "band-like" inflammation, cytoplasmic vacuolization in basal keratinocytes and basal apoptotic (*cytoid* or *civatte*) bodies, commonly unseen in chronic laryngitis. The hyperkeratotic appearance of laryngeal LP can also mimic squamous cell carcinoma, which should be always ruled out, since LP can be successfully treated with glucocorticoid-based therapy,

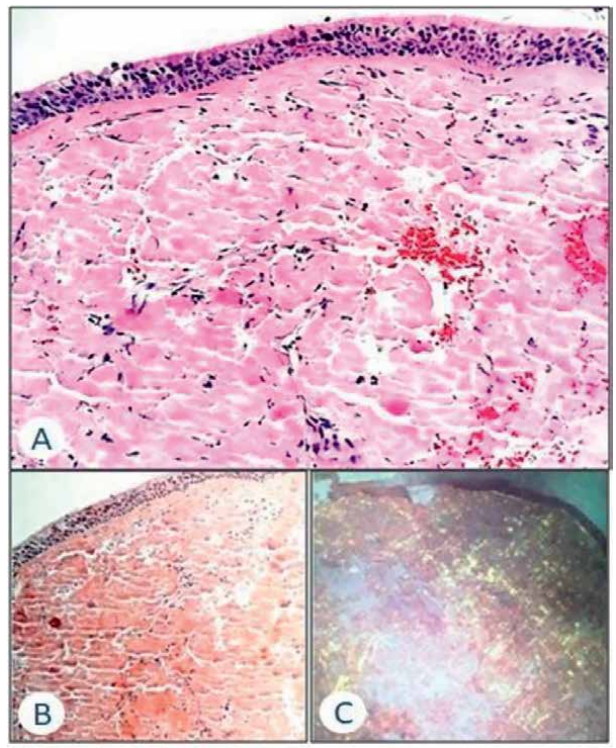

Figure 3.
A. Amyloid deposition beneath the mucosal surface in the ventricular region (hematoxylin–eosin, x10 magnification); B. Congo red dye under white light microscopy (x10 magnification); C. note the diagnostic apple-green refraction under polarized light microscopy (x10 magnification).

avoiding unnecessary surgical procedures [14]. Among systemic diseases potentially involving the larynx, amyloidosis should be also mentioned. It consists of a disease group characterized by extracellular deposition of insoluble protein in tissues, known as amyloid fibers. Larynx can be involved in both the system and localized amyloidosis. In the localized variant the laryngeal location is not uncommon, accounting for about 15% of cases, being the glottic region the most involved laryngeal site. At fiber-optic examination, a raised whitish plaque can be detected. Histological examination is useful to recognize the presence of amorphous material in the subepithelial connective tissue. Squamous hyperplasia is usually absent and, in contrast with other nonneoplastic causes of LL, the gross features of the lesions are related to the amyloid protein accumulation rather than to the epithelial thickening. The use of Congo Red dye is useful to highlight a green apple birefringence using polarized light microscopy (**Figure 3**) [15, 16].

4. Laryngeal leukoplakia and dysplasia

Laryngeal dysplasia (LD) is defined by a spectrum of both maturation abnormalities and nuclear atypia involving the laryngeal epithelial lining, that may or may not precede an invasive squamous carcinoma. Even though dysplasia includes atypical cellular features, such a term should not be considered synonymous with atypia, as the latter indicates atypical nuclear features alone, excluding the maturation abnormalities. Thus, the two terms should not be used interchangeably. Dysplastic changes encompass crowded immature epithelial cells, loss of cellular polarity, nuclear pleomorphism and hyperchromasia, increased nucleus-to-cytoplasm ratio, and mitoses including atypical forms. Such cellular and architectural abnormalities can be found as either superimposed into pre-existing squamous hyperplasia or raised into non-hyperplastic laryngeal epithelium. Hence squamous hyperplasia should not be considered a prerequisite for developing LD. According to the dysplasia model applied for the uterine cervix, LD is defined as mild, moderate, and severe regarding the level of epithelial involvement. In situ carcinoma (CIS-non-keratinizing type) is defined by the full-thickness mucosal epithelial dysplastic change without infiltration of the basement membrane. Conversely to the uterine cervix, the larynx usually harbors keratinizing dysplasia, which exhibits by definition at least focal squamous maturation, making the concept of a full-thickness dysplastic involvement not suitable for laryngeal CIS. As a consequence, the use of the term *severe keratinizing dysplasia* (SKD) is likely a more appropriate designation. Abnormal supra-basal maturation with dyskeratotic features, mitoses and surface keratinization are needed to qualify the histologic picture of LD as severe. Nonetheless, histopathologic criteria for evaluating laryngeal keratinizing dysplasia are less defined [17–20].

4.1 Grading systems

LD represents the earliest lesion manifesting, at both microscopic and molecular levels, neoplastic features [5]. Although the progression risk differs according to the grading, LD is widely considered the precursor lesion of squamous cell carcinoma (SCC). The LD grading has been a matter of disagreement among clinicians and pathologists, because of terminology was not uniform, grade designation seemed burdened by subjectivity and the risk stratification was often imprecise. The role of grading is mainly focused on the definition of the progression risk toward SCC. Squamous hyperplasia carries a very low risk of developing invasive SCC, whereas the presence of dysplasia increased such a risk [21]. In order to improve uniformity in diagnostic terminology,

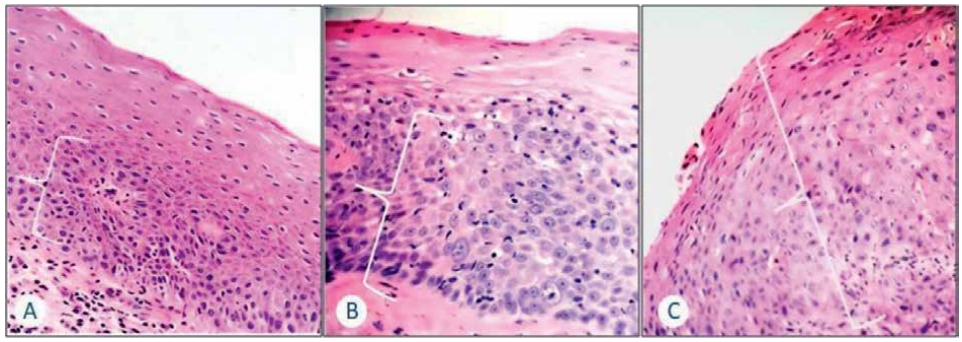

Figure 4.
Laryngeal dysplasia grading: A. mild laryngeal dysplasia, note that nuclear crowding, cellular atypia and abnormal maturation is limited to the lower third of the epithelial lining (, hematoxylin–eosin, x10 magnification); B. moderate laryngeal dysplasia, note that nuclear crowding, cellular atypia and abnormal maturation involve the lower half of the epithelial lining (hematoxylin–eosin, x20 magnification); C. severe laryngeal dysplasia, note that nuclear crowding, cellular atypia and abnormal maturation involve more than one half of the epithelial lining (hematoxylin–eosin, x20 magnification).

several grading systems and classification schemes have been proposed. It was previously suggested that *squamous intra-epithelial neoplasia* (SIN) was the most suitable term to refer to these epithelial changes since they are regarded as a morphologic manifestation of the noninvasive neoplasia [22, 23]. The Ljubljana Classification improved the concordance degree of histopathologic assessment of LD [24], even though the SIN classification system and the Ljubljana Classification were conceptually different, beyond their terminology. Subsequently, the concept of laryngeal intraepithelial neoplasia (LIN) was introduced, including both dysplasia and CIS. In 2017, the World Health Organization (WHO) recommended a two-tier classification, consisting of low and high-grade dysplasia/intraepithelial neoplasia, based on the severity of both architectural changes and cytological atypia, in order to improve the diagnostic reproducibility (**Figure 4**) [25, 26]. The concept of laryngeal CIS was introduced in the previous WHO classification (2005) and subsequently removed from the SIN classification, which considered both severe dysplasia and CIS in the SIN3 category. A transient reappraisal of CIS was seen in the amended version of the Ljubljana Classification, distinguishing the high-grade squamous intra-epithelial lesions (SIL) from CIS. Actually, laryngeal CIS has been included in the high-grade dysplasia, according to the latest WHO classification (**Table 1**).

Abnormal maturation	**WHO 2005**	**SIN classification**	**Ljubljana classification (amended version)**	**LIN classification**	**WHO 2017**
Basal third	Mild dysplasia	SIN 1	Low Grade SIL	LIN 1	Low Grade Dysplasia
Lower half	Moderate dysplasia	SIN 1 or SIN 2		LIN 2	
More than half		SIN 2	High Grade SIL	LIN 3	High Grade Dysplasia
Upper third	Severe dysplasia				
Full thickness	CIS		CIS		

Table 1.
Comparison of following grading systems for laryngeal dysplasia.

4.2 Carcinogenic mechanisms

Several causative agents and carcinogenic mechanisms have been suggested in SCC. The concept of *field cancerization* (FC) was introduced to describe pathologic atypia in epithelial cells surrounding oro-pharyngeal carcinomas. The role of multiple independent carcinogenic events involving different cells has been postulated, suggesting the role played by carcinogen activation on the whole exposed mucosa. Hence, mutant cellular clones can develop within that field giving rise to metachronous secondary tumors, that should be interpreted as secondary primary rather than recurrent tumors [27, 28]. The concept of FC was confirmed by further studies on head and neck SCC recurrences despite therapy [29, 30]. Alternatively, it has been proposed that neoplastic clones could spread laterally, running within the epithelial lining, from the site of the neoplastic primary toward adjacent normal mucosa [31–34]. Besides the oral cavity, FC has been described in the larynx, which can be exposed to tobacco smoke and other environmental carcinogens. Tobacco and alcohol consumption are the most important risk factors, implicated in 75% of all head and neck SCC [35, 36]. Recent molecular findings suggested that such a phenomenon could be promoted by the acquirement of genetic alteration in a cellular subset with stemness properties, giving rise to a clonal cellular progeny characterized by p53 mutation [37]. Moreover, some nutritional, environmental, and occupational factors were claimed to be implied in the development of head and neck malignancies [38].

The carcinogenic role of the *Human Papilloma Virus (HPV) infection* has been advocated as a causative agent in a subset of LD and SCC. More than 200 different HPV genotypes have been characterized and subclassified into low-, intermediate-, and high-risk types according to their carcinogenic potential. HPV infection was found to play a role in the earliest stage of carcinogenesis, but a direct causative effect lacked to be fully established in laryngeal SCC [39] Moreover, high-risk HPV (hr-HPV) DNA was also detected in healthy laryngeal tissue where it was considered a bystander [40]. The significance of HPV laryngeal infection lacks to be fully elucidated. The carcinogenetic role of HPV infection relies on the viral integration in the host genome

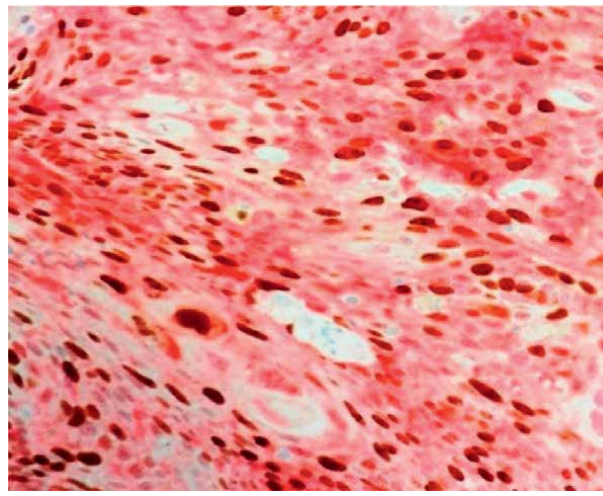

Figure 5.
Laryngeal HPV-related invasive SCC. Note the immunohistochemical $p16^{(red)}$ and $Ki67^{(DAB)}$ co-staining (x 40 magnification).

and disruption of intracellular control pathways. Indeed, the interaction of the viral subunits E6 and E7 with cell-cycle regulatory proteins p53 and retinoblastoma respectively has been established for integrated and transcriptionally active hr-HPV and contributed to promoting carcinogenesis [41, 42]. Low-risk genotypes such as HPV-6 and HPV-11 are related to recurrent laryngeal papillomatosis [43]. Despite the carcinogenetic role of HPV infection being a controversial topic in the larynx, the causative involvement of hr-HPV (e.g., HPV-16) in the pathogenesis of peculiar SCC subtypes, such as the verrucous [44] and papillary [45] variants have been reported [46, 47]. HPV-related SCC of the larynx and hypo-pharynx are mostly non-keratinizing cancers. In papillary SCC the prevalence of HPV infection is variable, and its oncogenic role remains a matter of concern [48]. Non-keratinizing SCC is an emergent variant of HPV-related laryngeal SCC. It is the most frequent histologic pattern in HPV-related SCC of the head and neck (**Figure 5**) [49]. In contrast with laryngeal SCC, the potential role of HPV infection in lung cancer is actually not supported [50].

5. Laryngeal leukoplakia and squamous cell cancer

Any neoplastic infiltration beyond the basement membrane into the underlying connective tissue should be referred to as invasive SCC.

The *micro-invasive* SCC is considered the earliest invasive lesion. It is defined by the presence of scattered malignant cells or discrete foci or tongues of neoplastic cells within the submucosa, just below the basement membrane. They are excluded from microinvasive laryngeal carcinomas both CIS, because non-invasive by definition, and those lesions show vascular invasion and muscle or cartilage involvement. Some authors established 1–2 mm as a cut-off to identify an SCC as microinvasive, others proposed the extension into the stroma by <0,5 mm, as measured from the basement membrane of the closest non-neoplastic epithelium [51–53]. The assessment of microinvasion on biopsy can be challenging because mucosal specimens could be superficial and not comprehensive of the invasive component. Thus, caution should be paid in excluding an invasive component when full-thickness malignant cells' replacement is seen on small biopsy specimens since it could lead to an underestimation of micro-invasive SCC. Furthermore, integrity gaps in the basement membrane alone do not stand for a micro-invasive carcinoma, as the evidence of neoplastic foci in the sub-epithelial connective tissue is a necessary diagnostic requirement. Once evaluated on biopsy, such findings should be accepted as noninvasive carcinoma with reservations, until the assessment of the full surgical excision [54]. Multiple sections of the whole surgical specimen should be examined to confidently rule out invasion. The colonization of seromucinous glands by dysplastic epithelial cells should not be misinterpreted as micro-invasion. Microinvasive SCC can be connected to the overlying dysplastic epithelium or not. The lack of such a morphologic continuum does not exclude the diagnosis of microinvasive SCC, as severe dysplasia is not a prerequisite for developing an invasive SCC, in the larynx as well as in the whole upper aerodigestive tract. The invasive nests must have unequivocable malignant cytological features and mitoses, including atypical forms.

The *superficially extending* SCC identifies a more advanced laryngeal lesion, invading beyond those histological limits introduced for defining microinvasion, without muscle or cartilage involvement [23]. The neoplastic invasion beyond the basement membrane makes the tumor capable of gaining access to the lymph-vascular channels, resulting in metastatic disease. A peculiar behavior is seen in glottic SCC, which

is usually not associated with metastatic spread in the early stage of disease compared to supra- and sub-glottis since this laryngeal compartment is characterized by a paucity of lymphatic drainage [55].

Invasive SCC is characterized by a spectrum of gross and histopathological features. Grossly, the larynx can harbor exophytic, flat, and ulcerated masses. From a histological perspective, both keratinizing and nonkeratinizing tumors can be found. Several growth patterns can be detected, ranging from conventional to papillary, verrucous, spindle cells, basaloid, and undifferentiated SCC. Neoplastic invasion can be characterized by both neoplastic cords or tongues attached to the superficial epithelium and scattered cells or dyscohesive neoplastic clusters in the lamina propria. Squamous differentiation can vary from well-differentiated to poorly differentiated forms. Association to CIS is not an uncommon finding.

5.1 Histological variants of laryngeal SCC

5.1.1 Papillary SCC

It affects men more than women. The larynx is the most common location, even though it can be seen in the oral cavity and hypopharynx. Papillary SCC usually occurs de novo since the occurrence of cancer at the site of previous papilloma has been rarely reported. The role of HPV infection has been established by in situ hybridization study in such cancer variants [56]. The tumor presented as an exophytic mass, histologically characterized by finger-like projections supported by fibrovascular cores or by a broad-based cauliflower-like growth pattern. Surface keratinization is usually scanty or absent, differentiating the papillary from the verrucous subtype of SCC. Cytologic malignant features are evident in the neoplastic epithelium of the papillary SCC, again differentiating it from verrucous SCC.

5.1.2 Verrucous SCC

It is a highly differentiated variant of SCC affecting men more than women, mostly in the laryngeal glottis. Tumor growth is locally destructive, without metastatic potential. Tobacco smoking and viral induction have been suggested as etiologic factors. The tumor presented as an exophytic mass, histologically characterized by a benign-appearing proliferation composed of uniform squamous cells without significant atypia nor mitoses, prominent surface *warty-like* keratinization, and a broad base with pushing-type margins. A mixed chronic inflammatory cells infiltrate can be seen in the stroma. Hybrid tumors composed of conventional and verrucous SCC have been described in the head and neck [57].

5.1.3 Spindle cells SCC

It is a highly aggressive biphasic tumor composed of both SCC (CIS or invasive) and spindle cells malignant neoplasm, affecting men more than women. In the larynx, both the glottis and the supra-glottic region can be involved. Previous irradiation has been involved as a risk factor, whilst there was no significant correlation with tobacco smoking, alcohol consumption, and occupational/environmental factors [58, 59]. Spindle cells SCC are not related to HPV infection [60]. Tumor mass usually presents as exophytic neoplasm consisting in a malignant undifferentiated spindle cells proliferation with SCC nests. The spindle cells' component

usually predominates, and it is characterized by prominent cytological atypia and frequent mitoses, often associated with necrotic foci. The growth pattern can vary from fascicular to storiform and palisading. Areas of stromal collagenization and myxomatous degeneration can be seen. Heterologous elements could be detected, mostly consisting of chondro- and osteo-sarcomatous foci. Epithelial derivation is supported by the intimate relationship with conventional SCC and by epithelial markers' expression. Spindle cells were found to express cytokeratins in the majority of cases, even though vimentin expression and myogenic differentiation have been reported [18, 60, 61]. Overall, spindle cells SCC usually behave malignantly, even though flat and ulcerating lesions have a worse prognosis if compared to exophytic variants [62]. Reactive myo-fibroblastic proliferations, mucosal malignant melanomas, and sarcomas should be considered in the differential [63–65].

5.1.4 Basaloid SCC

It is a high-grade variant of SCC involving palatal tonsils, tongue, hypopharynx, and larynx, the latter being mostly affected in the supraglottic region. Known etiologic factors are tobacco smoking and alcohol consumption. Tumor grossly presents as a firm whitish mass, associated with central necrosis. Basaloid cells, characterized by atypical hyperchromatic nuclei and scanty cytoplasm, increased mitotic activity, and peripheral nuclear palisading, are intermingled with conventional SCC. Mucohyaline stromal deposition can be seen. Basaloid cells usually expressed epithelial markers, even though Vimentin could be expressed in a subset. Adenoid cystic and neuroendocrine carcinoma should be considered in the differential [66, 67].

5.1.5 Undifferentiated (lymphoepithelioma-like/nasopharygeal type) SCC

Undifferentiated (lymphoepithelioma-like/nasopharygeal type) SCC can rarely affect larynx and hypopharynx. Such tumors resulted more prevalent in the Chinese population and related to EBV infection. At histology, keratinizing and nonkeratinizing forms have been described, being the latter further subdivided into differentiated and undifferentiated types [68].

5.2 Molecular prognostic markers

The risk of progression is known to vary in dysplastic LL according to the grading of dysplasia [69, 70]. The use of biomarkers to highlight the cumulative effect of genetic mutations can aid in a more accurate establishment of progression in LL. Prognostic biomarkers can be subdivided into four categories: (1) proliferation; (2) cell cycle control; (3) cell adhesion and invasion; (4) immune checkpoints. Malignant cells are known to acquire a high proliferative rate, that can be monitored by using several markers. Ki67 is a nuclear protein widely studied as proliferative marker, even though it does not represent a reliable marker of malignant transformation in laryngeal dysplasia [71–74]. TP53 is a well-established tumor suppressor gene involved in head and neck SCC. The loss of wild-type p53 activity, as well as p16 and cyclin D1, were frequently detected in many cancer types and were found to be involved in tumor progression [75, 76]. A specific isoform of CD44 (CD44v6) was established to interact with Osteopontin, which is known to be elevated in many cancer types and correlates with laryngeal SCC progression in the larynx [73]. Beta-catenin protein is coded by CTNNB1 gene and is involved together with E-cadherin in intercellular adherence

and epithelial structure maintenance. Alteration in beta-catenin protein expression plays a role in cancer progression and invasiveness [77]. In the past few years, tumor inflammatory microenvironment has gained more attention. In that setting, both tumors devoid of immune infiltrates and others marked by abundant T cell infiltrates have been detected. Programmed cell death protein 1 (PD1/CD279) is a member of the CD28 family of T cell co-stimulatory proteins that includes CTLA-4, ICOS, and BTLA. It has two specific ligands PD-L1 (B1-H1/CD274) and PD-L2 (B7-H2/CD273) which down-regulate T cell activation on binding to PD1. The PD-1/PD-L1 interaction represents a critical immune checkpoint in the adaptive immune resistance of SCC. Immunohistochemical assays have been employed to evaluate the expression of immune checkpoints in the tumor microenvironment, but limitations have been outlined by many authors, including the use of different antibody clones (including 5H1, E1L3N, SP142, 28–8, 22C3, SP142, and SP263) and the lack of a standardized scoring system. [78–80].

6. Conclusions

The clinical management of LL is a daily critical challenge for Otolaryngologists, who must be aware of the broad spectrum of pathological conditions that could underlie leukoplakia. An effective clinical-pathological correlation represents the basis for proper treatment planning in such patients.

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Conflict of interest

The author declares no conflict of interest.

Author details

Giuseppe Leoncini
First Division of Pathology, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

*Address all correspondence to: giuseppe.leoncini@istitutotumori.mi.it

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Chapter 6

Laryngomalacia

Vaishali Waindeskar, Pooja Thaware, Garima Chamania, Anuj Jain and Ashutosh Kaushal

Abstract

Laryngomalacia is the most common cause of stridor in neonates and infants. In laryngomalacia, there is a supraglottic collapse of the larynx during inspiration leading to obstruction and thus resulting in stridor. The exact etiology of laryngomalacia is still unknown. The neurological basis is one of the leading theories explaining the etiology. Laryngomalacia in most of the patients resolves with conservative management by two years of age. In severe cases of laryngomalacia or when symptoms are persistent beyond two years of age, such cases need surgical management in the form of supraglottoplasty. Flexible fibreoptic laryngoscopy is the gold standard for the diagnosis of laryngomalacia. Various classifications have been proposed to classify laryngomalacia, although considering dynamic airway changes might be the most acceptable basis for classification. Supraglottoplasty has higher success and a low complication rate.

Keywords: flexible fiberoptic laryngoscopy, Laryngomalacia, larynx, stridor, Supraglottoplasty

1. Introduction

Laryngomalacia is the most common cause of stridor in neonates and infants. In fact, laryngomalacia is the common cause of stridor in 60–70% of newborns and infants which makes laryngomalacia the most common congenital laryngeal anomaly [1]. Supraglottic collapse produced by certain anatomic variants causes airway obstruction in Laryngomalacia, which is most severe during inspiration. Flexible fiberoptic laryngoscopy is used to diagnose laryngomalacia. The general course is benign, with stridor progressing for 6 months until gradually disappearing by 12–24 months of age. The majority of cases resolve with minimal or no treatment. Of all the laryngomalacia patients, only ten to fifteen percent patients will have significant upper airway obstruction symptoms, including increased breathing effort, feeding difficulties, and failure to thrive. Supraglottoplasty is recommended in such severe situations.

The larynx is subdivided into three parts supraglottis, glottis, and subglottis. The supraglottis is the part between the inferior boundary of the hyoid bone and the vestibular folds. Therefore, the structures present in the supraglottis area are the epiglottis, arytenoid cartilages, and aryepiglottic folds. Laryngomalacia affects these supraglottic structures.

The pediatric airway is different from that of adults in many ways. The relatively large tongue in relation to the oropharynx, therefore pediatric patients are more likely to sustain airway obstruction under anesthesia due to relatively large tongue. The larynx is located more cephalic in the neck in neonates and infants. This high cephalic position helps to facilitate spontaneous breathing right after birth and prevents aspiration. The epiglottis is short, stubby and omega-shaped, angled over the vocal cords. Also, the infantile laryngeal cartilage is more flexible than older children and adults, which is a probable cause of collapsible characteristics of the neonatal and infantile larynx.

2. Signs and symptoms

The most common symptom in infants with laryngomalacia is positional stridor. Stridor commonly appears in the first few days of life, although children may not seek medical help until they are many months old. Stridor is usually worse in the supine position, particularly during crying or eating, because such activities necessitate increased respiratory efforts. The severity of symptoms increases during several months of infancy but usually resolves by two years of age and often earlier [2].

Although stridor is a common symptom of laryngomalacia, it is not often the cause of presentation to the medical facility. Sometimes patients with severe disease present with other respiratory complaints such as respiratory distress, use of accessory respiratory muscles and hypoxemia. Laryngomalacia can also present with atypical symptoms like snoring, obstructive sleep apnea and difficulty in swallowing. Although incidence and distribution of these atypical presentations are yet to be established [3]. Difficulty in swallowing causes decreased intake and respiratory distress increases metabolic demand thus can lead to failure to thrive in infants with laryngomalacia.

The natural history of laryngomalacia and that it resolves during the second year of life is supported by the low level of evidence and lacks endoscopic evidence. The time range within which laryngomalacia resolves and the proportion of patients in which laryngomalacia do get spontaneously resolved is yet to be answered. Atypical presentations are to be further explored. Therefore, prospective longitudinal trials are required to better understand the natural history of laryngomalacia [4].

Laryngomalacia in older children presents with obstructive sleep apnea syndrome. Other reasons in older children for seeking medical attention are exercise-induced stridor and dysphagia [5].

3. Etiology

The exact etiology and pathophysiology of laryngomalacia are still unknown. Multiple causal theories of laryngomalacia have been proposed. The neurological basis is one of the leading theories, which states that the abnormal integration of the laryngeal nerves leads to altered laryngeal tone. This theory has been supported by a pathologic study that has shown increased diameter of supraglottic nerve in patients with severe laryngomalacia. Another theory proposes an imbalance of demand and supply during inspiration as a cause of congenital laryngomalacia. This theory of imbalance needs further study. Acid reflux disease has not been established as a cause of laryngomalacia, although almost 60% of infants who present with laryngomalacia

also have accompanying acid reflux disease. Acid reflux disease causes irritation and thus edema of the upper airway which further worsens laryngeal obstruction.

In the scenario of debated etiologies of laryngomalacia, a neurological basis is considered as the most probable etiology of laryngomalacia among all the theories mentioned before. Another case report supporting the neurological basis is a unique case report where a child who was diagnosed case of moyamoya disease suffered acquired laryngomalacia following a neurologic insult. The child suffered a cerebrovascular accident following which she developed laryngomalacia presenting with severe stridor and chest retractions and a nocturnal oxygen requirement, and severe laryngomalacia being noted on laryngoscopy. Prior to the cerebrovascular accident, she had no symptoms of laryngomalacia and had undergone several laryngoscopies, both awake and anesthetized, which showed no evidence of laryngomalacia [6].

Children with laryngomalacia showed vitamin D deficiency and increased proinflammatory cytokine IL-6, which may result from dysregulation of the immune responses. Laryngomalacia could be an inflammatory disease secondary to maternal deficiency of 25(OH)-vitamin D with subsequent Vitamin D deficiency in exclusively breast-fed infants during neonatal and infantile periods [7].

4. Factors that influence disease severity

The patient factors that influence disease severity are Apgar score at birth and during the first several minutes after birth, resting oxyhemoglobin saturation level at the time of presentation, and the presence of a secondary airway anomaly. Additional co-morbidities in children with laryngomalacia increases disease severity and also affect the prognosis of surgical outcome. Such co-morbidities can be gastroesophageal reflux disease, laryngopharyngeal reflux, neurologic disease, congenital heart disease, genetic syndrome, or anomaly.

Patients with severe laryngomalacia will require surgery. Patients who have gastroesophageal reflux disease or laryngopharyngeal reflux and one additional co-morbidity are more likely to require revision supraglottoplasty. Those with three medical co-morbidities are more likely to require tracheostomy [8].

5. Classification of laryngomalacia

There are a number of classifications of laryngomalacia. A simple and well-detailed classification of laryngomalacia by Olney et al. describing type 1, type 2, and type 3 laryngomalacia as prolapsing arytenoids, shortened aryepiglottic folds, and prolapsing epiglottis [9]. The classification of Olney et al. is simple, but covers only about two-third of laryngomalacia cases and also mixes static and dynamic findings.

Van der Heijden et al. after studying various laryngomalacia classifications have proposed a Groningen Laryngomalacia Classification System (GLCS) which is based on the photo and video documentation of eighty five patients diagnosed in a tertiary referral centre combined with a review of the literature [10].

This simplified system is supposed to ease communication among professionals and provide a base for treatment algorithms. In laryngomalacia, there is a collapse of the supraglottic airway during inspiration causing obstruction. This is a dynamic change of the airway happening during inspiration. Some previous classifications

were based on static findings. Anatomical findings such as omega-shaped epiglottis, short aryepiglottic folds and acutely angled epiglottis over laryngeal inlet are static findings. In laryngomalacia obstruction is due to dynamic change in the airway, and static findings do not completely explain these dynamic changes and therefore are not the excellent choice for the classification of laryngomalacia. McSwiney et al. were the first to introduce a system in order to classify laryngomalacia and it was based on static findings [11]. McSwiney et al. further combined omega-shaped epiglottis and posterior displacement in one single type of laryngomalacia, suggesting omega shaped epiglottis is exclusively associated with posterior displacement of the epiglottis. Although, omega-shaped epiglottis can also present in conjunction with medial displacement of aryepiglottic folds during inspiration. Holinger et al. divided laryngomalacia into six different types, with static and dynamic findings described as separate entities. Shah et al. exclusively described dynamic changes but the definitions of the different types of laryngomalacia were insufficiently described [12]. Kay et al. use a system in which Type 1 is defined as static finding and Type 2 as a dynamic finding and type 3 is a collection of "all other etiologies" including neuromuscular disease, which renders the classification less reliable [13]. None of these systems discussed here are widely accepted. Classifications require simplification in such a way that they not only provide a genuine classification based on dynamic findings but also allow making a righteous decision for the intervention required.

The Groningen laryngomalacia classification system is a newly proposed classification system exclusively based on dynamic laryngeal changes. In Groningen's laryngomalacia classification, laryngomalacia is divided into three types; Type 1 is inward collapse of arytenoid cartilages, Type 2 is medial displacement of aryepiglottic folds, and Type 3 is posterocaudal displacement of epiglottis against the posterior pharyngeal wall.

The GLCS has also proposed the probable surgical intervention for each category required. They suggested that the decision between surgical management and conservative strategy should be based on the severity of laryngomalacia, and when surgical management is planned, the GLCS can suggest the surgical intervention required. The surgical intervention suggested for Type 1 laryngomalacia of GLCS is the removal of redundant mucosa over arytenoids with or without the removal of cuneiform or corniculate cartilage. In Type 2 laryngomalacia suggested intervention is incision or excision of a wedge of aryepiglottic folds. In Type 3, epiglottopexy would be the surgical intervention required. However, these treatment options should be clinically individualized for each patient.

Kay et al. also provided a classification-based treatment algorithm. They discerned three types in which type I is recommended to be treated by dissection of the aryepiglottic folds, type II by resection of redundant mucosa over arytenoid cartilage, but cases with "all other etiology" were supposed to receive tracheostomy.

6. Diagnosis

A thorough physical examination of the infant should be performed, with special attention to the oral cavity, nose, and neck. A complete birth history is required, including any surgical history or intubations performed on the patient. Parents should inform about any breathing problems children may have at home, with a

focus on noisy breathing or apnea episodes. Laryngomalacia is characterized by noisy breathing that worsens with meals or while lying supine. The clinician should investigate the patient's eating habits and keep track of any weight loss or failure to thrive.

It's important to ensure choanal patency and rule out piriform aperture stenosis. A complete oral cavity examination is required to rule out cleft lip or cleft palate, glossoptosis, Pierre-Robin sequence, or micrognathia, all of which can cause breathing and feeding difficulties. A thorough examination of the neck is also required to rule out any tumors or vascular abnormalities. Hemangiomas with a beard-like distribution should be given special attention, as these infants are more prone to have hemangiomas in the airway. In order to properly evaluate a patient with suspected laryngomalacia, a flexible laryngoscopy examination of the supraglottic airway in an awake newborn is required. The infant should be transferred to the operating room for a diagnostic bronchoscopy if the examiner notices serious symptoms.

Flexible fiberoptic laryngoscopy is the mainstay in the diagnosis of infant stridor. It permits the real-time visualization of the aerodigestive tract during spontaneous ventilation. It allows complete visualization of the oropharynx, hypopharynx, supraglottis, glottis and subglottis. Due to the simplicity and ability to thoroughly examine the dynamic collapse of the supraglottic airway during awake respiration, flexible fiberoptic laryngoscopy is presently the gold standard for the diagnosis of laryngomalacia.

Direct laryngoscopy and diagnostic bronchoscopy in the operation theater give the clinician a complete evaluation of the upper aerodigestive tract to the level of carina and the mainstem bronchi. It is a valuable procedure principally in patients with severe symptoms or in patients who have concomitant secondary airway anomalies. Surgical intervention is also possible with direct laryngoscopy when warranted.

Radiologic studies might be helpful in the diagnosis of swallowing difficulty. A modified barium swallow examination is preferred in infants with laryngomalacia since aspiration may be silent and not detectable clinically.

A polysomnogram is beneficial in determining the presence and severity of obstructive sleep apnea, particularly in older children. To improve the apnea-hypopnea index in such children surgical intervention like supraglottoplasty might be beneficial.

Airway fluoroscopy due to low sensitivity and exposure to ionizing radiation is not advocated in the assessment of infant stridor.

7. Management

Most of the children of laryngomalacia can be managed conservatively as the symptoms usually disappear by the end of the second year of life. In the majority of cases, laryngomalacia is a self-limiting condition. Only 5–20% of children with severe laryngomalacia undergo surgical intervention. As mentioned before transoral supraglottoplasty has a low complication in otherwise healthy children [14]. To reduce inspiratory obstruction in laryngomalacia, redundant tissue in the upper airway is cut and/or the aryepiglottic folds are loosened in bilateral supraglottoplasty. While bilateral supraglottoplasty is generally well tolerated, about 10% of individuals experience side effects such as laryngeal edema, new-onset aspiration, or supraglottic stenosis. Supraglottic stenosis is a life-threatening condition that is difficult to treat surgically.

A few clinicians have reported performing unilateral supraglottoplasty to lessen the risk of problems associated with bilateral surgery.

For the treatment of severe laryngomalacia, Walner et al. advocated a staged approach to bilateral supraglottoplasty [15]. Staged supraglottoplasty implies a unilateral supraglottoplasty on the most affected side, followed by, if necessary, an opposite-side operation week to months later. For the surgery, they used cold steel instruments, with or without the use of a microdebrider.

In the staged approach first stage of surgery involves the removal of the redundant tissue on the most affected side using either straight or curved microscissors. Then to release the ipsilateral aryepiglottic fold a small wedge of tissue was removed. Microdebrider can also be used to remove redundant tissue overlying the arytenoid cartilage on the most affected side, and then a small wedge of tissue from the aryepiglottic fold on the same side can be removed after using microscissors. Afrin-soaked pledgets were used on the cut surfaces to reduce bleeding. Walner et al. further describe that after surgery all patients were extubated and monitored for 24 hours prior [15]. Patients were reevaluated for symptoms after 4 to 6 weeks. If the problems of breathing or feeding continued, the second step of surgery was employed to provide further relief. An opposite-side supraglottoplasty was performed, with redundant arytenoid mucosa excised and the aryepiglottic fold released on the side opposite to the original surgery. If aryepiglottic fold on the side previously operated appears to be too tight it was re-released. According to Walner et al., 73% of individuals who underwent the first stage of surgery had considerable improvement or resolution of stridor, while 100% of those who underwent the second stage had significant improvement or resolution of stridor. There were no complications in any of the patients.

Low-temperature plasma radiofrequency ablation (LTP-RFA) is another surgical therapy option. According to the severity of laryngomalacia, Hongming Xu et al. presented the first prospective four-arm randomized trial to compare the efficacy and short outcomes of patients with moderate and severe laryngomalacia who were randomly treated with LTP-RFA, traditional surgical supraglottoplasty, or wait-and-see policy [16]. When compared to typical surgical supraglottoplasty, LTP-RFA treatment dramatically reduced operating time, length of hospital stay, and amount of intraoperative hemorrhage in children with severe laryngomalacia, but treatment efficacy was equivalent. In addition, when compared to the control group, LTP-RFA treatment dramatically alleviated laryngomalacia symptoms in children with moderate laryngomalacia. Post-operative pneumonia was the most common consequence, affecting 11% of patients.

8. Anesthesia

Choice of ventilation strategy is the main concern for the anesthesia team in the case of laryngomalacia. The following are the ventilation strategy that can be utilized [17]:

a. Spontaneous breathing is the choice of ventilation with experienced anesthesia and surgeon teams.

b. Controlled mechanical ventilation using a small internal diameter endotracheal tube is nowadays used rarely, as the tube interferes in the vicinity of the surgical site.

c. Intermittent apnea technique is another choice for ventilation under anesthesia but surgery needs to be interrupted in between for manual ventilation when the patient desaturates and thus surgeon gets limited time duration in between two ventilations.

d. Jet ventilation can sometimes be used for this surgery.

9. Conclusions

Laryngomalacia despite the fact that it is a self limiting disease, caregivers must recognize severe cases. A child's growth may be hindered in severe cases of laryngomalacia due to breathing and feeding difficulty. Laryngomalacia is resolved in more than 90% of cases after supraglottoplasty, which enhances the child's quality of life. Only in a few cases a second surgery is required to resolve residual symptoms.

Conflict of interest

The authors declare there are no conflict of interest.

Acronyms and abbreviations

GLCS	Groningen Laryngomalacia Classification System
LTP-RFA	Low-temperature plasma radiofrequency ablation

Author details

Vaishali Waindeskar, Pooja Thaware*, Garima Chamania, Anuj Jain and Ashutosh Kaushal
Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Bhopal, India

*Address all correspondence to: pthaware20@gmail.com

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Chapter 7

Approach to the Difficult Airway in Laryngeal Cancer

Maria Elena Buenrostro Espinosa, Samantha Rivero Borrell, Jorge Francisco Piña Rubio, Maria Fernanda Ochoa Cortez, Lesle Hernandez Uvence and Liz Marlene Montes Sandoval

Abstract

The laryngeal cancer is the second most frequent neoplasm of the upper aerodigestive tract. In these patients, the incidence of difficult airway is very high, and sometimes the anatomy can be modified because of the previous treatments like radiotherapy, making difficult intubation and difficult mask ventilation. To prevent an emergency, it is a priority to make an approach plan, appropriate preoperative assessment, have the necessary tools, and work together with the surgical team.

Keywords: airway management, laryngeal neoplasms, laryngectomy, video laryngoscope, difficult airway

1. Introduction

The incidence of difficult airway in patients with head and neck cancer is higher than in the general population. Particularly, cancer of the larynx, which is the second most frequent neoplasm of the aerodigestive tract, represents a real challenge for the anesthesiologist, since he deals with patients with tumors at any stage and in elective or emergency situations.

2. Laryngeal cancer

Of head and neck tumors, laryngeal cancer accounts for 50% with a higher incidence in men than woman with a 4:1 ratio. The three major locations for laryngeal cancer are glottis (59%), followed by the supraglottic area (40%) and the subglottic area (1%) [1]. Laryngeal stenosis, fistula formation, local recurrence, and adjacent lymph node metastasis are some of the complications that the patient can develop in long term [2].

Laryngectomy is an effective cancer procedure and is associated with good functional outcomes. The current UK standard of care for locally advanced malignancy is aimed at organ preservation. This is for patients with T3 tumors on the tumor-nodes-metastases (TNM) scale. For patients with T4 disease invading the laryngeal

cartilages, total laryngectomy is recommended. Although laryngeal preservation may seem preferable, these cases require careful discussion at a regional head and neck cancer multidisciplinary team meeting, as evidence is emerging that patients who undergo primary surgery have improved survival rates. Long-term complications of oncological treatments may ultimately result in a "frozen larynx," where the patient requires a tracheostomy and gastrostomy, or even ultimately a laryngectomy to prevent aspiration. National guidelines recommend that laryngectomy is performed in specialist centers, as complication rates are lower in departments that perform this procedure frequently [3].

Organ preservation is recommended in patients with T3 tumors on TNM classification (tumor, nodule, metastasis), and total laryngectomy is indicated in T4 patients with invasive disease to laryngeal cartilages. Although preserving surgery may seem better, all cases require careful analysis to perform the procedure that improves survival rates. We can see complications of oncological treatments; for example, "frozen larynx," in these cases the patient requires tracheostomy and gastrostomy, or even a laryngectomy to prevent aspiration. National guidelines recommend that laryngectomy is performed in specialist centers, as complication rates are lower in departments that perform this procedure frequently [3].

The context in which the anesthesiologist can find the patient is in elective or emergency situations, as well as in early or advanced stages. The most challenging aspect would be the intubation of the post-radiotherapy patient. It is important to understand the disease process and the management of these cancers, because a proper anesthetic management plan will be decisive. There must be open lines of communication with surgeon and wider team for better results [3].

Based on the knowledge of the possible occurrence of difficult ventilation, all the associated necessary equipment should be ready for an instant application, and also, additional measures such as preparation of emergent tracheostomy, cardiopulmonary resuscitation, and airway management following ASA guideline may be implemented [2].

3. Difficult airway

Difficult airway is defined as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation, difficulty with tracheal intubation, or both. Situations of "cannot intubate and cannot ventilate (CICV)" may occur in 0.01–0.07% of patients undergoing surgery. This is a true emergency situation. This situation must be resolved as soon as possible, so that a harmful outcome does not occur like permanent brain damage or death. Spontaneous breathing must be restored, if is not possible then the surgical access of the airway must be done [4].

The anatomical modifications due to the disease as well as morphological changes by previous treatments (radiotherapy and chemotherapy in the head and neck cancer patients) are responsible for the difficulties in the airway. The incidence of difficult intubation ranges from 0.5 to 2% in the general population, from 8 to 10% in patients having ears, nose, and throat surgery, and rises to 28% in patients with tumors of the airway [1, 5]. Glottic cancers are the commonest (50–60%). These patients present difficulties due to the presence of mass, a receding jaw, restricted mouth opening, and neck movement or due to associated comorbidities. The size and location of tumor are the crucial factors in determining the appropriate approach to the airway [1].

4. Preoperative assessment

The characteristics that are most often observed in the patient who has head and neck cancer are the following: elderly, chronic consumer of ethanol, and/or a smoker. broncho-pneumopathie chronique obstructive, pulmonary emphysema, ischemic coronary heart disease, high blood pressure, chronic hepatopathy with toxic etiology, coagulopathies are associated with the oncological status [6].

Some patients have nutritional disorders due to the difficulty in swallowing due to the presence of the tumor, which leads to weight loss, anemia, and dyselectrolytemia. All these alterations should be corrected as far as possible before undergoing surgery [6].

Preoperative evaluation should include full blood count, clotting screen, biochemical profile with urea and electrolytes, liver function test, blood sugar, and electrocardiography. Other studies that should be considered in some patients are chest X-ray, pulmonary function tests, arterial blood gases, and echocardiogram, because some may have chronic obstructive pulmonary disease or some cardiopathy associated with their risk factors [7].

It is common to find chronic obstructive pulmonary disease (COPD) in head and neck cancer patients so modification of bronchodilator therapy, steroids, and treatment of acute infection can optimize patient conditions [7].

Laryngeal cancer treatment includes surgery, chemotherapy, and radiotherapy, and these treatments may worsen airway management. Radiation therapy after the primary surgery may lead to immobility of the mandible and neck. A careful examination of the área between the hyoid bone and submentum is required, because we can detect risk factors for difficult airway. For some patients, even with normal mentohyoid distance, the larynx might be located much more anterior than normal, due to radiotherapy-induced fibrosis in the submandibular área, and this factor makes intubation difficult. Some side effects of radiation therapy, for example, dermatitis and oral mucositis, can make the tissue more susceptible to infection, and bleeding may occur during airway management. The patient may present local edema due to damage to the lymphatic ducts after radiotherapy. Preoperative tracheostomy sometimes becomes indicated when a difficult airway is evident before surgery or after previously performed laryngeal surgery [2].

We should evaluate the mouth opening, mallampati score, laryngoscopic view at previous operations, neck movement, and prominent teeth, and look for masses in neck, scarring from previous surgery, and immobility of the larynx from previous radiotherapy.

Cross-sectional imaging techniques are the most useful in confirming intrinsic compression of the airways, a feature that may not be appreciated on endoscopic analysis alone [8]. It is indicated to identify the extension of the tumor and the potential obstruction through imaging studies, radiological imaging with computed tomography or magnetic resonance imaging can help. In experienced hands, ultrasonography is useful in identifying the cricothyroid membrane before induction of anesthesia to have identified the surgical access in case of emergency (**Figure 1**) [7].

Awake nasal endoscopy can be carried out before induction of anesthesia and is especially useful when no other radiological investigations are available. It gives a real-time view of the upper airway and the larynx [7].

Preoperative nasoendoscopy can determine the airway diameter, detailed evaluation of the airway, location, size, nature and mobility of tumor (e.g., pedunculated), bleeding and edema, the epiglottis and glottis, vocal cord movement, pooling of secretions, it does not require more than a simple preparation of the nose with a local

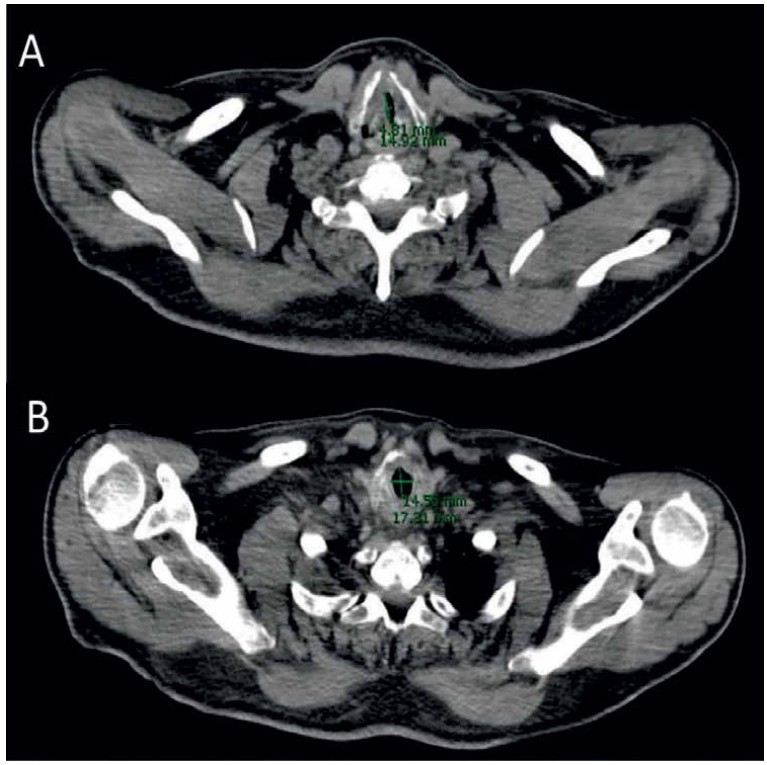

Figure 1.
A. Computed tomography with axial section showing maximum glottic narrowing caused by tumor. B. Subglottic region, with less compromise in the tracheal diameter.

anesthetic and a vasoconstrictor, and it is very important to identify a potential airway obstruction [8] and is useful in identifying patients in whom an awake technique or conscious fibroscopic-assisted intubation is more appropriate [2, 7]. In short, it allows us to examine the condition of larynx and pharynx.

Before starting surgery, the following points should be defined:

i. Ventilation with a face mask will be possible?

ii. Laryngoscopy is going to be difficult?

iii. Intubation (passing the tube through the glottis) is going to be difficult?

iv. An awake technique is more appropriate?

v. It is possible to make a surgical airway and front of neck access (FONA) is feasible?

When you should consider awake intubation? When difficulty in tracheal intubation and bag-mask ventilation is predicted or has been experienced previously. When performing a technique with an awake patient, you have an advantage because you maintain the permeable airway, gas exchange, and protection against aspiration during

the intubation process. General anesthesia makes the airway more difficult with more obstruction, making identification of landmarks difficult on endoscopy [7].

It is essential for the anesthesiologist to prevent an emergency situation and make the right decision for the safety of the patient; therefore, a plan must be formulated.

5. Planning airway management

Procedures performed on patients with laryngeal cancer ranges from panendoscopy and biopsy to laryngectomy and occasionally emergency tracheostomy [3]. And the planning of airway management should be performed for elective patient and elective surgery and for those who may present in extremis with stridor.

Evaluation of the airway includes history and bedside examination, review of imaging and nasendocopy findings as well as discussion with the surgical team.

It is essential to bear in mind other rescue oxygenation techniques, in case the primary plan fails. The rescue plans may include ventilation with face mask or supraglottic devices, and also a surgical airway. The team must consider that insertion and placement of supraglottic airway devices are difficult in patients with reduced opening of the jaw, oropharyngeal lesions, and after radiotherapy. In these cases, intubation using a supraglottic airway as a conduit is difficult or even impossible so we must consider these risk factors before performing the anesthetic induction.

Because of the high incidence of anticipated difficult airways in head and neck patients, it is prudent to seek video-assisted laryngoscopy as the primary technique, video laryngoscopes have emerged as a common first-line option for laryngoscopy, and the Difficult Airway Society (DAS) highlights its role in difficult intubation. A 93–96% first-attempt intubation success rate can be achieved with acute-angle video laryngoscopes such as the Glidescope or CMAC Storz systems, reducing the number of patients at risk of intubation failure.

Direct laryngoscopy (DL) exposes the laryngeal inlet under direct vision and requires a direct line of sight to align airway axes (oral-pharyngeal-laryngeal) for optimal glottic visualization. Oftentimes, manipulations to align these axes include head extension, neck flexion, laryngeal manipulation, and other stressful movements [9]. Videolaryngoscopy (VL) optimizes first-attempt success when compared to direct laryngoscopy, and utilizes indirect laryngoscopy *via* its camera; glottic visualization is better, and the need for a direct line of sight to visualize airway structures is eliminated. VL requires the application of less force to the base of the tongue, reduces time to intubate, and lessens hemodynamic response to intubation when compared with the traditional direct visualization technique [9].

Evidence has made it clearer that videolaryngoscopy eases intubation difficulty and increases first-attempt success rates in the airway predicted to be difficult to intubate by direct laryngscopy.

Awake fiber-optic intubation is the safest approach to managing difficult airways, and it can be extremely helpful in patients with supraglottic obstruction (e.g., epiglottis, tongue, basal obstructions, intraoral masses), but it is not the first-line option in patients with a narrow laryngeal inlet or with tumors that cause obstruction at the laryngeal level, which may fail due to the inability to displace the tumor or simply because the tube cannot be advanced and thus precipitates a total obstruction [7].

Active oxygenation strategies must be present throughout the difficult airway management process. One of them is apneic oxygenation.

Trans-nasal high-flow rapid insufflation ventilatory exchange or THRIVE is an oxygenation technique that provides heated and humidified oxygen using high-flow nasal cannula. This system has recently been shown to increase the apnea time in head and neck patients including those with stridor. Trans-nasal high-flow rapid insufflation ventilatory exchange combines apneic oxygenation, continuous positive airway pressure and flow-dependent dead space flushing, which overcomes airway obstruction and increases safety margin during sedation. THRIVE provides up to 70 L/min of oxygen and is well tolerated because of humidification. It changes the nature of difficult intubations from a hurried process to a more controlled event, with an extended apneic window and reduced iatrogenic trauma [3].

The mainstay method of increasing the apneic window is through pre-oxygenation, which entails spontaneous facemask ventilation with 100% oxygen [10]. Pre-oxygenation denitrogenises the lungs and creates an alveolar oxygen reservoir. The physiological phenomenon that occurs is called aventilatory mass flow (AVMF) or apneic oxygenation. A patent air passageway exists between the lungs and the exterior, and the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH2O that drives oxygen into the lungs. This could extend safe apnea time during prolonged laryngoscopy and intubation.

6. The obstructed airway

Inspiratory stridor suggests a reduction in airway diameter at the supraglottic, periglottic, or glottic level of at least 50%. Expiratory stridor originates at or below the glottis level, which is characteristic of tracheal or tracheobronchial narrowing, while inspiratory-expiratory (biphasic) stridor generally points to obstructive subglottic disease [11].

We have to define the group of patients who are being considered with stridor at rest. In this group, the stridor is due to a reduction in airway diameter of at least 50%. Patients with slow-growing tumors often present late. So when we meet patients classified in this small group, we know that we will face a tumor of important measure.

Perilaryngeal tumors include supraglottic, pharyngeal, pyriform fossa, epiglottic, vocal cord, and subglottic lesions.

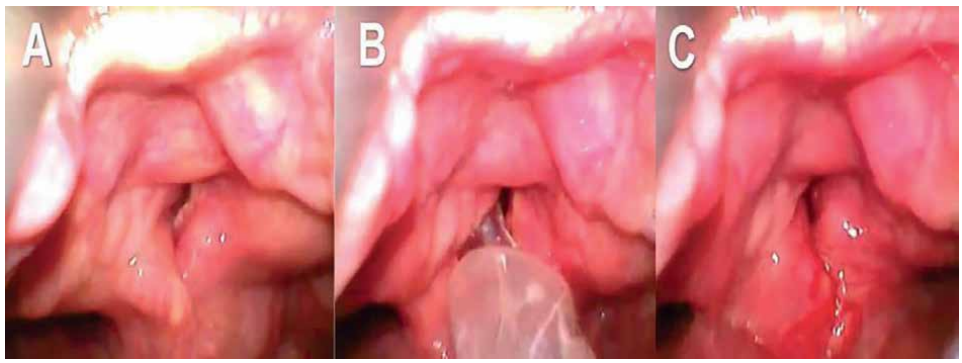

Figure 2.
A. Videolaryngoscopy images show a narrowing at the level of the glottis. B. decreased diameter, and inability to pass a #5.5 DI orotracheal tube. C. Friable and bleeding tumor.

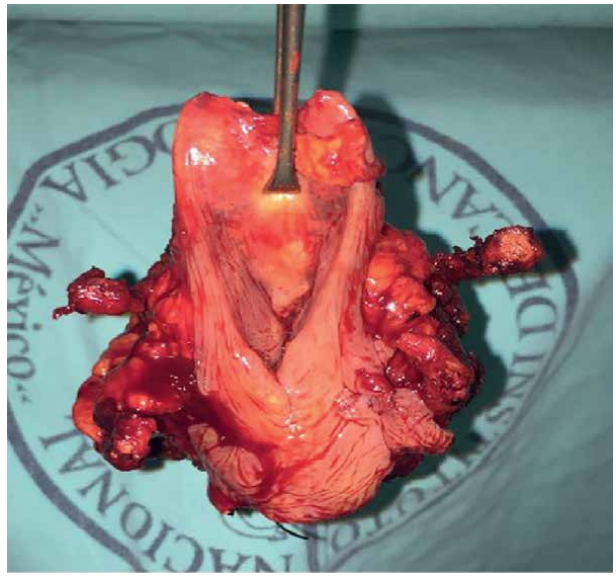

Figure 3.
Total laryngectomy in laryngeal cancer.

The patient should be asked whether, in addition to having noisy breathing, he has actually experienced difficulty in breathing; in particular, has he woken at night in a panic. The presence of nocturnal symptoms usually indicates that there is more advanced obstruction [11].

Patients with significant stridor at rest can be divided broadly into two groups: (1) those in whom intubation is considered possible and (2) those definitely requiring preliminary local anesthetic tracheosomy [11].

The patient, who comes to hospital for the first time as an emergency, is usually the one who will needs a local anesthetic tracheostomy. Severe disease will generally manifest with nocturnal respiratory difficulties and panic attacks [11]. The patient with less severe obstruction is referred to an outpatient clinic (**Figures 2** and **3**).

7. Other anesthetic considerations

It is required to identify patient at risk of airway obstruction because intravenous or inhalational induction may precipitate airway obstruction due to tumor bulk. Even local anesthesia is not without risk because severe airway obstruction precipitated by laryngospasm has occurred [12].

Is polemical the use of muscle relaxant drugs sometimes facilitates laryngoscopy but in other cases is controversial because of the greater risk of airway obstruction. Current practice has also been influenced by new intubation devices such as video laryngoscopes [12].

If tracheal intubation is considered possible, the main options are an inhalational induction with direct laryngoscopy and tracheal intubation, or an awake fiber-optic intubation. Supraglottic tumors may cause obstruction when intravenous induction and muscle relaxation are used. Intravenous induction of anesthesia and the use of a muscle relaxant are not recommended in this situation [8].

The objective of an inhalational induction is to preserve spontaneous ventilation until adequate depth of anesthesia is obtained and direct laryngoscopy and visualization of the glottis is allowed [8]. Sevoflurane is used and allows rapid, smooth induction of anesthesia, and has the benefit of lack of airway irritation and low blood gas solubility. The disadvantages that can be presented are coughing and laryngospasm upon instrumentation, and sometimes respiratory obstruction when the patient loses consciousness to the beginning of the anesthesia.

When anesthetic depth is adequate, laryngoscopy is undertaken and a rapid decision is made as to whether intubation is possible. If a laryngoscope does not provide an adequate view of the glottis, a second attempt may be made with a different instrument or a different approach, for example, video-laryngoscope. A rigid bronchoscope may be used by an experienced person.

If after laryngoscopy and under direct vision, the anatomy is difficult to visualize or the glottic opening is very small, which is prudent to let the surgeon perform the tracheostomy without haste; but if it is decided to intubate, it must be made a maximum of two attempts. Repeated laryngoscopies have a risk of generating bleeding in necrotic and friable tumors, and this may lead to a total obstruction of the airway, and lead to a situation of "I cannot intubate" "I cannot oxygenate." If the laryngoscopy fails, the team must be informed and continue with the planned plan [7].

The prolonged manipulation of the upper respiratory tract can cause cardiovascular responses: bradycardia, tachycardia, hypertension, cardiac arrhythmias, and is important to consider.

The way to ensure the airway in the postoperative of head and neck cancer surgery is with a tracheostomy. When orotracheal or nasotracheal intubation is not possible or a major surgical intervention for oral cancer with reconstructive tissue transfer is planned, the better option is an elective tracheostomy in a conscious patient [6].

Tracheostomy as an approach method of the airways is obligated in patients with tumors located in the larynx or below the glottis with obstructive effect, and also in cases of laryngeal stenosis or significant supraglottic edema. Tracheostomy should not be made in pediatric patients because the trachea is small with a soft cartilage and difficult to palpate [6].

8. Postoperative

A careful strategy should be planned for the extubation of those patients who do not require postoperative tracheostomy.

After prolonged surgery, we can find some issues, for example, swelling, bleeding, and airway debris. If tracheal intubation was difficult in the first place, reintubation is likely to be more. Other strategies may also be used: trans-tracheal catheters and airway exchange catheters. An airway exchange catheter is a long, small internal diameter, hollow, semi-rigid catheter that is inserted through an *in situ* endotracheal tube prior to extubation. The patient tolerates the catheter and facilitates rapid reintubation if needed [8].

It is essential that anesthetists are aware of human factors, maintain situational awareness, avoid task fixation, and do not resort to unfamiliar techniques. A coordinated team approach with clear communication is essential [6].

9. Conclusions

Difficult airway can lead to serious complications in head and neck cancer surgical patients, specifically in cancer of the larynx.

The anesthesiologist should need a careful planning for intubation and extubation of difficult airway depending on surgery and conditions of the patient.

The use of appropriate airway equipment, oxygenation techniques, surgical airway access, all options must be available to rescue a difficult airway.

Intubation of the patient with laryngeal cancer is a challenge that must be addressed through a team approach. Management will depend on clinical presentation, individual experience, and equipment availability.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Maria Elena Buenrostro Espinosa[1*], Samantha Rivero Borrell[2], Jorge Francisco Piña Rubio[3], Maria Fernanda Ochoa Cortez[4], Lesle Hernandez Uvence[5] and Liz Marlene Montes Sandoval[6]

1 Oncological Anesthesia, IMSS Mexicali, México

2 Oncological Anesthesia, Hospital Angeles del Carmen, Jalisco, México

3 Neuroanesthesiologists, Hospital ISSSTECALI Mexicali, B.C, México

4 Anesthesiologists, Hospital ISSSTECALI Mexicali, B.C, México

5 Bioengineer, Resident of Anesthesiology, Hospital ISSSTE Mexicali, B.C, México

6 Resident of Anesthesiology, Hospital ISSSTE Mexicali, B.C, México

*Address all correspondence to: buenrostro.espinosa@gmail.com

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Chapter 8

Adenoid Cystic Carcinoma of Larynx

Tarang Patel and Garima Anandani

Abstract

Salivary gland tumours are rare tumours of larynx, hypopharynx and parapharyngeal space. Adenoid cystic carcinoma (AdCC) is the most common malignant salivary gland tumour of larynx. Subglottic region is the most common site followed by supraglottic region. AdCC usually involves elderly patients. Etiology of AdCC is mostly unknown. Clinically patient presents with dysphagia, cough, dyspnoea, hoarseness and rarely haemoptysis. Indirect laryngoscopy shows submucosal laryngeal mass. On CT scan, there is a submucosal mass, which may show extra-laryngeal extension. Histopathological examination shows epithelial and myoepithelial cells arranged in cribriform pattern, which may present with perineural invasion in the periphery of the lesion. Patients usually present in a later course of the disease. Tumour may present with pulmonary metastasis. The surgical approach depends on the tumour stage.

Keywords: adenoid cystic carcinoma, larynx, minor salivary gland tumour, cribriform pattern, perineural invasion, local recurrence

1. Introduction

Adenoid cystic carcinoma (AdCC) was first described in 1853 and thereafter underwent multiple modifications of names before it was given the current name of AdCC in 1930 by Spies [1, 2]. AdCC is an epithelial malignant neoplasm predominantly involving minor and major salivary glands [3]. Malignant tumours involving minor salivary glands are rare and consists of 2–4% of all the head and neck malignancies [4]. Minor salivary gland tumours commonly occur in the oral cavity, peculiarly in the hard palate, with an occasional occurrence in the nasal cavity, paranasal sinuses, pharynx and larynx, correlating with the usual distribution of minor salivary glands in the head and neck region [4, 5]. AdCC is a rare tumour comprising of <1% of all cancers of head and neck. Out of all salivary gland tumours, AdCC accounts for 7.5–10% [6–10]. Minor salivary gland tumours of larynx are very rare, constituting less than 1% of laryngeal tumours [11].

Laryngeal AdCC accounts for 0.07–0.25% of all laryngeal tumours, and hypoglottis is the most common laryngeal site to be involved [5, 8, 12]. Laryngeal AdCC originates from subepithelial minor salivary glands [13]. There is usually no sexual predilection for laryngeal AdCC [10, 14]. Spread through perineural invasion is common [15].

Patients of laryngeal AdCC commonly present with a complaint of dyspnoea. Rarely do patients present with loco-regional metastasis. The average survival of patients is about eight years, and the evolution of prognosis depends on local recurrence and metastasis to lung, bones and brain [12, 16].

2. Discussion

The most common laryngeal malignancy is squamous cell carcinoma; however, other epithelial, mesenchymal and neuroendocrine tumours are rare in this location [16, 17]. Laryngeal salivary gland carcinomas are rare because density of minor salivary glands in larynx is very low, about 23–47 glands per cm^2. Laryngeal salivary gland malignancies comprise less than 1% of all laryngeal malignancies, the most common being AdCC [18, 19]. No definite risk factors have been identified for laryngeal AdCC [20]. Smoking affects laryngeal AdCC in the same way as it affects squamous cell carcinoma [21]. Sub-glottis (64%) is the most common site to be affected, followed by supra-glottis (25%), trans-glottic (6%) and glottic (5%) regions [22].

2.1 Etiopathogenesis and genetic profile

The definite aetiology of AdCC of larynx is not known to date. However, according to recent research, genomic changes are the cornerstone of aetiology for the development of malignant salivary gland tumours including AdCC. The most common genomic changes are a chromosomal translocation t(6;9) or very rarely a translocation t(8;9), which result in fusion of MYB or MYBL1 oncogenes with NFIB transcription factor gene [23]. Recent findings suggest that t(6;9) led to the fusion of MYB exon 14 to NFIB coding exon. This caused deletion of MYB exon 15, which contains many regulatory genes. The loss of MYB gene regulation leads to the overactivation of crucial MYB target genes involved in apoptosis, cell growth, cell cycle control and cell adhesion [24, 25]. West et al. suggested that MYB-NFIB translocation is specific for AdCC and it is not present in any other salivary gland tumour [26]. Cytogenetic studies have demonstrated that AdCC tumour is derived from various differentiated salivary gland tissues undergoing dedifferentiation and lead to early developmental gene profile [27, 28]. Microarray study found that AdCC is associated with genes of myoepithelial differentiation and high levels of SOX4 transcription factor along with overexpression of casein kinase-1 epsilon and frizzled-7 involved in the Wnt/β-catenin pathway [29–31].

2.2 Clinical features

These tumours often occur in elderly patients usually in 6th or 7th decades. However, they can occur at any age ranging from 10 to 96 years [21, 32]. There is generally no gender predilection [10, 14]; however, according to a few researchers, there is a slight preponderance in females [21, 32]. It is clinically characterized by indolent and slow growth [1]. Mostly tumour goes undetected, until the involvement of local structures and local nerves, which may cause variable symptoms depending on the site involved [33]. Clinical features correlate with tumour size and location. Patients with glottic tumours present with dyspnoea or hoarseness, whereas supraglottic tumours present with dysphagia. Patients with glottic and supraglottic tumours are diagnosed at an early stage due to the early detection of

symptoms [4, 5]. Subglottic tumours often present with difficulty in breathing, cough and stridor at a later stage. Due to the submucosal spread of laryngeal AdCC, it is often tough to diagnose AdCC at an early stage [5, 16, 21]. Hence, most of the patients are diagnosed at a later stage of the disease [20]. There is neurological involvement along with local infiltrative growth penetrating the nerve, lymphatics, blood vessels, muscle and bone [34]. AdCC metastasis to cervical lymph nodes is rare, seen only in about 10–15% of cases of head and neck AdCC [35]. Previous reports suggest that AdCC presents with distant metastasis in 35–50% of cases, lung being the most common site followed by bone and liver [4, 14, 36, 37].

2.3 Radiological findings

If dyspnoea persists even after adequate therapy, radiological examination such as computerized tomography (CT) scan is necessary for an exact assessment of the tumour [16, 38]. CT scan is also of crucial importance in accurate pre-operative evaluation. It can assess the primary tumour site, extra-luminal spread, local spread and distant metastasis. However, sometimes AdCC may be difficult to be diagnosed on CT scan because of submucosal spread of laryngeal AdCC in absence of any apparent mass. CT scan with contrast medium can be used in difficult cases [21]. FDG-PET scan shows variable uptake in case of AdCC depending on the differentiation and grade as compared to squamous cell carcinoma, which usually shows high uptake [39]. FDG-PET scan expresses high sensitivity in cases of residual/recurrent tumour or local metastasis of AdCC (**Figure 1**) [40, 41].

2.4 Pathological findings

2.4.1 Gross examination

Grossly tumour is usually firm and poorly circumscribed. Tumour size ranges from 1 to 8 cm. Tumour size more than 3 cm is usually related to increased rate of distal metastasis [42]. Cut surface is grey-white, firm to soft, and very rarely haemorrhage and necrosis which may suggest high-grade variant of tumour or dedifferentiated AdCC (**Figure 2**) [1, 43].

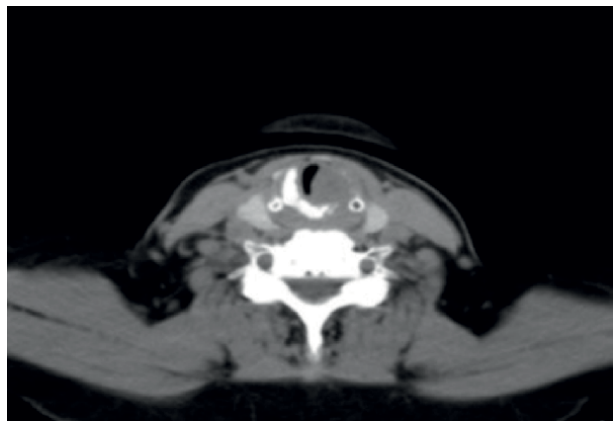

Figure 1.
CT scan of larynx showing a mass involving the left vocal cord along with infiltration of adjacent cartilage.

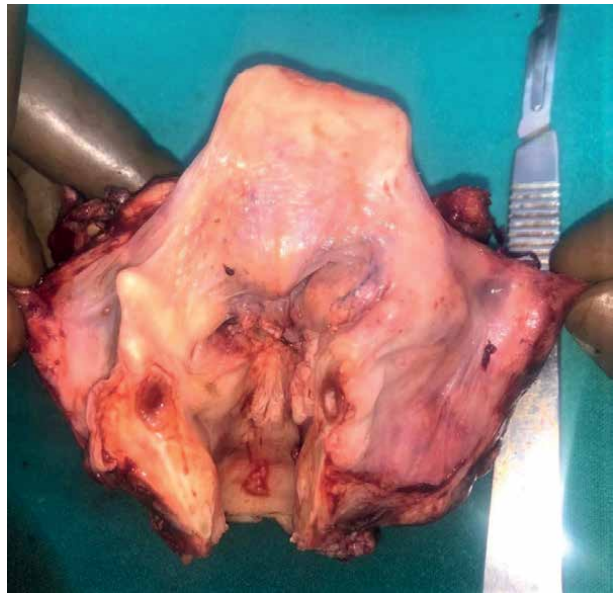

Figure 2.
Specimen of total laryngectomy showing right-sided glottic mass on gross examination.

2.4.2 Microscopic examination

Microscopy shows basaloid malignant tumour encompassing a mixture of epithelial and myoepithelial cells. Histopathological classification is mainly divided into three types: solid, cribriform and tubular [44–46]. Cribriform pattern is the most common histological pattern characterized by islands or nests of basaloid cells interrupted by punched out spaces, which form 'sieve-like' or 'swiss-cheese' pattern [47, 48]. These cystic spaces are not true glandular lumina and they are continuous with the stroma surrounding them. The characteristic eosinophilic periodic-acid-schiff (PAS) positive basement membrane material is present in the pseudocyst [1, 47, 48]. Some tumour cells show true glandular lumina along with pseudocysts. Tumour cytology shows relatively uniform basaloid appearing cells with hyperchromatic angulated nuclei and scant cytoplasm [1]. AdCC is notorious for increased tendency for perineural invasion (PNI). AdCC showing perineural invasion is so common that in absence of invasion of perineurial spaces, diagnosis of AdCC is doubtful [49].

Some AdCC show mainly tubular growth, some may have predominantly solid patterns, and very rarely sclerosing pattern may be seen [50–52]. Solid variant is characterized by tumour cells arranged in sheets without the formation of lumen or pseudocysts and may consist of admixture of epithelial and myoepithelial cells. A solid component may show increased mitosis and cytological atypia along with foci of necrosis [23, 53]. Dedifferentiated or high-grade transformation of AdCC may be rarely seen, which consists of conventional AdCC along with dedifferentiated components in the form of poorly differentiated adenocarcinoma or undifferentiated carcinoma. High-grade components lack any ductal or myoepithelial differentiation and show increased mitosis (>5/HPF), comedo-necrosis and focal squamoid growth (**Figure 3** and **4**) [43].

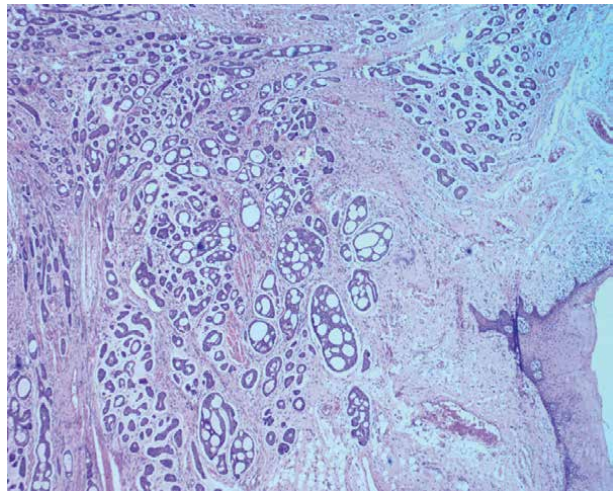

Figure 3.
H&E stained sections from the excision biopsy showing submucosal proliferation of tumour cells arranged predominantly in cribriform and tubular pattern (100×).

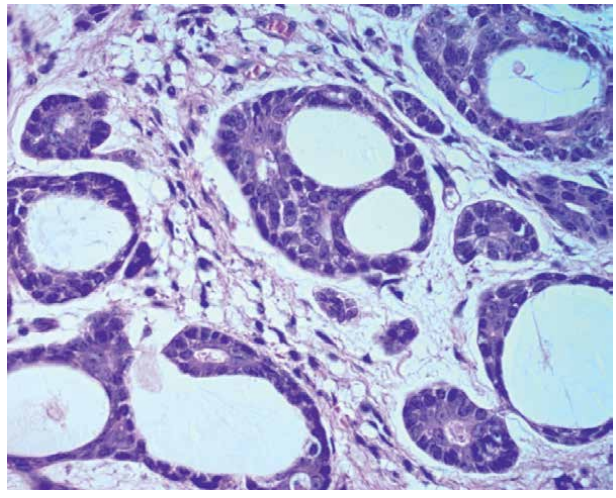

Figure 4.
H&E stained sections from the excision biopsy showing basaloid cells having angulated hyperchromatic nuclei with punched out spaces containing basement membrane material (400×).

Immunohistochemistry (IHC) or electron microscopy study revealed that tumour cells of AdCC depict either myoepithelial or intercalated ductal differentiation [54]. Tumour cells in the region of ductal cells express markers of intercalated duct phenotype, showing positivity for CD117 (c-kit), CEA, keratin and lysosome. Tumour cells adjacent to cystic spaces show myoepithelial markers in form of immunopositivity for p63, S-100 and actin [54–56]. Cytogenetics studies demonstrate loss of heterozygosity at chromosome 6q23-35 [57]. TP53 mutations are very rare except in a few cases of dedifferentiated AdCC [58].

Major diagnostic entities need to be differentiated from AdCC, including polymorphous adenocarcinoma, pleomorphic adenoma and basal cell adenoma/

adenocarcinoma. Polymorphous adenocarcinoma is also common in minor salivary gland, but it is negative or only focal positive for c-KIT. Pleomorphic adenoma is a benign encapsulated tumour with frequent chondromyxoid stroma, whereas AdCC is invasive tumour with foci of PNI [56]. Basal cell adenoma and basal cell adenocarcinoma predominantly arise in major salivary glands [1].

AdCC is graded in accordance with the percentage of solid components seen microscopically. Grade I tumour is composed of predominantly tubular and cribriform patterns. Grade II tumour shows cribriform and tubular pattern with less than 30% solid component and Grade III tumour consists of more than 30% solid tumour area [59]. Solid component of AdCC usually acts as a predictor of poor prognosis [33, 60]. However, grading can be difficult as a single tumour may be composed of variable patterns of more than one subtype. According to few reports, staging using American Joint Committee on Cancer (AJCC) is more useful to predict prognosis and distant metastasis [32, 61]. During staging, documentation of PNI is crucial because infiltration of major nerve has been associated with a poorer prognosis compared to infiltration of minor nerve [62, 63].

2.5 Treatment

Surgical excision in form of total laryngectomy is the preferred treatment for localized AdCC, which ultimately results in complete resection of the tumour with negative surgical margins, without compromising the function of the affected organ [64–66]. Modified radical neck dissection is performed only in cases of positive cervical lymph nodes [64]. Post-operative recurrence rates usually range from 30 to 75% [67].

To minimize the risk of relapse or recurrence, post-operative radiotherapy (PORT) may be administered [63, 68, 69]. Five-year and ten-year local control rates are higher in patients treated with surgery and PORT compared to those patients treated only with surgery [67, 70, 71]. After complete resection in T1 and T2 tumours, radiotherapy (RT) is recommended in intermediate or high-grade AdCC. Cases of T3 and T4 tumours in presence of clinically positive lymph nodes, PNI and positive surgical margins are treated with adjuvant RT. The dose recommended in PORT is >60 Gy in high-risk patients and >44 Gy in low- to intermediate-risk patients [72]. Primary definitive RT is recommended in patients with unresectable tumour mass [68, 72]. Chemotherapy is useful along with surgery in cases of high-grade tumours or to prevent metastasis. It is also recommended in advanced cases of distant metastasis [16, 21, 72].

It is hypothesized that vascular endothelial growth factor receptor (VEGFR) plays an important role in tumour angiogenesis and AdCC pathogenesis of AdCC. The expression of VEGF by the tumour cells correlates with tumour size, staging, invasion of blood vessels, risk of recurrence and distant metastasis. VEGF-A also acts as a downstream regulator of MYB expression. So VEGFR signal inhibition in the tumour may be useful in suppressing the tumour growth and blood flow [29, 73, 74]. Anlotinib, a tyrosine kinase inhibitor against VEGFR-1,-2,-3, and Lenvatinib, a multiple kinase inhibitor against VEGFR-1,-2,-3 kinases have shown effective results as a molecular target therapy for AdCC [72, 75, 76].

Definitive tumour grading and TNM staging along with reporting of perineural invasion and status of surgical margins are the principal prognostic factors. Ki-67 and p53 markers further add details regarding tumour grade and prognosis. Post-therapy close and long-term follow-up are required to ascertain any tumour relapse or distant metastasis [77].

3. Conclusions

Laryngeal minor salivary gland carcinomas are very rare, comprising <1% of all the malignancies of larynx. Laryngeal AdCC should be kept in mind in cases of locally aggressive laryngeal tumours, particularly when a patient is not at risk for the development of squamous cell carcinoma. Most of the patients are diagnosed at a later stage of the disease. Pre-operative diagnosis is usually confirmed by microscopy. Surgical excision with clear margins with or without RT is recommended for management. Recurrence or distant metastasis of laryngeal AdCC can be detected by regular post-operative follow-up. Identification and study of new molecular markers underlying AdCC pathogenesis, such as c-KIT and VEGFR may help in the development of targeted therapy.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AdCC	Adenoid cystic carcinoma
MYB	Myeloblastosis
MYBL1	MYB Proto-Oncogene Like 1
NFIB	Nuclear factor 1 B-type
SOX4	SRY-related HMG-box
CT	Computerized Tomography
FDG	Fluorodeoxyglucose
PET	Positron Emission Tomography
PAS	Periodic-acid- Schiff
PNI	Perineural invasion
HPF	High power field
IHC	Immunohistochemistry
CD117	Cluster of differentiation 117
CEA	Carcino-embryonic antigen
p63	Protein 63
TP53	Tumor Protein 53
AJCC	American Joint Committee on Cancer
H & E	Hematoxylin and Eosin
RT	Radiotherapy
PORT	Post-operative radiotherap
Gy	Gray
VEGFR	Vascular endothelial growth factor receptor

Author details

Tarang Patel* and Garima Anandani
All India Institute of Medical Sciences (AIIMS), Rajkot, India

*Address all correspondence to: tarangpatel_86@yahoo.co.in

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Section 5

Laryngeal Airway Surgery

Chapter 9

Challenges in Tracheostomy

Sapna S. Nambiar, Slimcy Shylen and Suma Radhakrishnan

Abstract

Tracheostomy is a life saving procedure of placement of a surgical airway. It is imperative for every medical personnel to be conversant with it as it helps secure airway, the first step in resuscitation when necessary. It is not only thorough knowledge of the anatomy of the neck and procedural technique but also the awareness of the unusual challenging situations likely during this procedure that can help avoid complications and enable one to be better prepared for any eventuality. This chapter aims to draw the attention to the likely challenges during tracheostomy including pediatric tracheostomy and percutaneous dilatational tracheostomy. An encounter with pseudoneurysm of the internal carotid artery helps understand the gravity of the likely challenges that a surgeon must be prepared to manage.

Keywords: tracheostomy, pediatric tracheostomy, percutaneous dilatational tracheostomy, pseudoaneurysms of internal carotid artery

1. Introduction

Tracheostomy, the placement of a surgical airway, is a life saving procedure when endotracheal intubation is not an option or fails. Today with advancements in technology most patients can be easily intubated with very few absolute indications for tracheostomy. Patients' with severe maxillofacial injuries following road traffic accident and deep neck space abscess with impending airway obstruction are two of the glaring examples where emergency tracheostomy is the preferred option to secure airway. In the past, the primary reason for the placement of a surgical airway was emergent due to an impending airway obstruction, inability to intubate, or inability to ventilate with a bag mask [1]. A patient with stridor having a definitive contraindication for endotracheal intubation requires tracheostomy immediately. An otorhinolaryngologist is required many a times to perform this procedure either in the casualty or emergency operation theater itself. Now, elective placement is much more common with advances in emergency airway management. However it is not always possible to have the requisite expertise and advanced equipments required for the airway management. Also, there are several instances where the placement of a surgical airway is recommended, especially in the setting of large tumors of the upper aerodigestive tract, laryngotracheal injuries that preclude intubation, inflammatory swelling of the upper airway, bleeding in the airway, maxillofacial trauma, bilateral vocal cord immobility, and so on. Furthermore, in settings of known difficulty with intubation or certain facial dysmorphisms, an elective surgical airway is ideal [2]. Therefore it is not only necessary to have a thorough knowledge of the anatomy of

the neck and procedural technique but it is also equally essential to know the unusual challenging situations one can face during this procedure to avoid complications and be better prepared.

This chapter aims to draw the attention to likely challenges in tracheostomy which can help the surgeon be better prepared in such situations and it can help one to be fore warned prior to the procedure in order to avoid likely complications.

2. History of tracheostomy

Tracheostomy is a procedure that has been performed as early as in 100 BC with documentation by the Greek physicians. It has gone through the mentioned 5 periods-

i. Period of legend- 2000 BC to 1546 AD

ii. Period of fear - 1546 AD to 1833 It was performed only by a brave few at the risk of their reputation

iii. Period of drama – 1833 to 1932 Gradually it came to be considered as the preferred means to secure airway in emergency situations in acutely obstructed patients.

iv. Period of enthusiasm – 1932 to 1965 where the adage, "If you think of tracheostomy.....do it!!" became popular.

v. Period of rationalization – 1965 to till date where the merits of tracheostomy and intubation have been debated for good.

However with the advancements in technology and use of it in early diagnosis of airway lesions it has become possible to plan the definite treatment early and avoid unnecessary tracheostomies. The bronchoscopic guided intubation has further eased the procedure even in difficult scenarios. Therefore we now enter an era of dealing with challenges in the procedure; "period of challenges" as we prepare ourselves to be aware of the challenges and tackle them reducing mortality and morbidity.

3. Challenges during tracheostomy

The neck dissection can be challenging in many situations like advanced laryngeal, hypopharyngeal malignancies, thyroid malignancies, deep neck space abscess, post radiation recurrence in neck etc. It is essential to ascertain the site of obstruction and evaluate the pulmonary status prior to the procedure. Tracheostomy would be futile in case of obstructions below the level of the planned stoma in the trachea. Based on the site; tracheostomy is classified as: High, Mid and Low tracheostomy. Usually it's the mid tracheostomy that is done at the level of the isthmus of the thyroid gland i.e. between 2nd and 3rd or 3rd and 4th tracheal rings. The low tracheostomy done below the level of the isthmus does carry the risk of injury to great vessels or damage to the pleura thereby resulting in pneumothorax and hence one must be careful. Usually the opinion of cardiothoracic surgeon is taken where sternotomy is required to approach the trachea like in enlarged thyroid with retrosternal extension or anaplastic thyroid

carcinoma with stridor. The ideal timing (early vs. late) and techniques (percutaneous dilatational, other new percutaneous techniques, open surgical) for tracheostomy have been topics of considerable debate. Based on evidence from 2 recent large randomized trials, it is reasonable to wait at least 10 d to be certain that a patient has an ongoing need for mechanical ventilation before consideration of tracheostomy [3]. However emergency tracheostomy is a life saving procedure required to be done within minutes with high complication rate as one does not have the luxury of time to ensure adequate preparation. This is where one must be well versed and equipped to deal with challenges.

4. Relevant anatomy

The anatomy of the trachea must be understood with its relations to other relevant structures in the neck. The trachea is a 10 to 15 cm long fibro cartilaginous tube that begins at the inferior border of the cricoid cartilage at the level of the sixth cervical vertebra (C6), about 5 cm above the jugular notch. The inspection of the neck is important as patients with short neck, contractures post burns, post irradiated necks, severe cervical spondylosis, enlarged thyroid gland can pose difficulties during tracheostomy (**Figure 1**). The proper positioning of the patient ensuring good extension of neck is necessary to make the trachea more prominent and superficial to help in easy location and faster dissection especially during emergency tracheostomy. It is needless to emphasize the importance of good lighting in the field of dissection with an equally efficient assistant during the procedure as the structures must be well retracted to help locate the trachea in the midline. Midline dissection especially during emergencies can help one remain in the relatively avascular plain but this is not always true. The identification of the thyroid gland with appropriate dissection away from the plane of surgery by either hooking it up or in difficult cases ligating and dividing the isthmus can help reach the trachea faster. The pretracheal fascia is identified and confirmation of trachea done by aspirating air into a syringe with 4% lignocaine which can then be injected in case of procedures being done under local anesthesia. Once identified the inter cartilginous incision with or without removal of a part of the anterior tracheal wall is carried out to then introduce the tracheostomy tube of appropriate size while keeping the lumen open using the Trousseau's tracheal

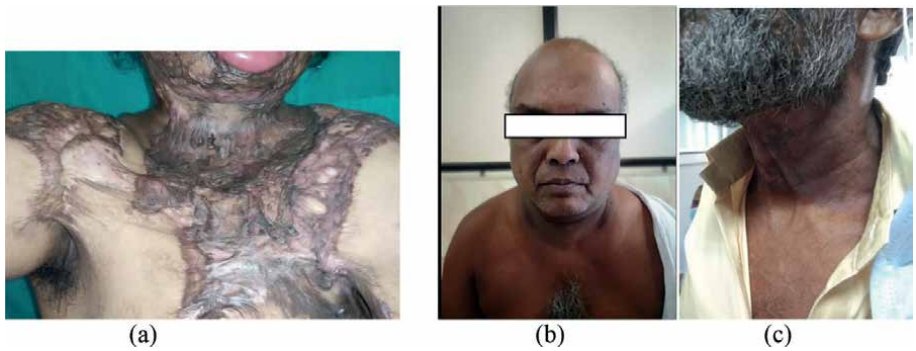

Figure 1.
Neck findings that can pose difficulties during tracheostomy (a) scar post burns, (b) short neck and (c) post irradiated neck.

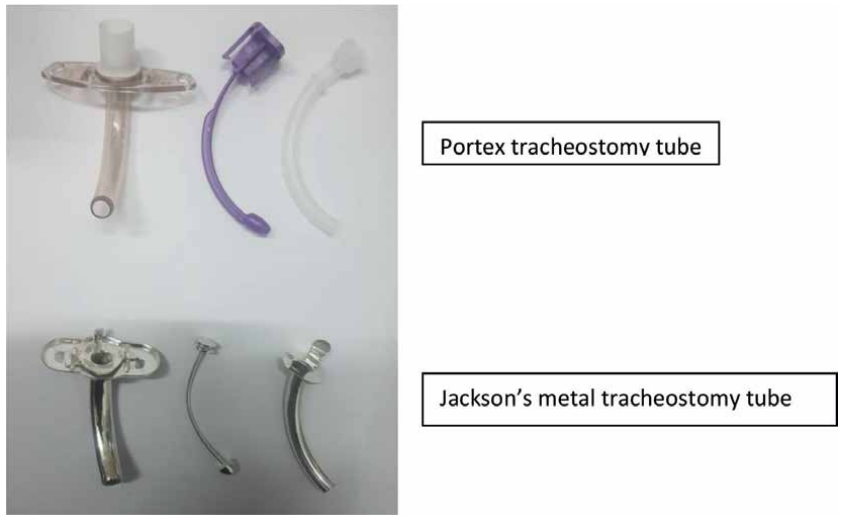

Figure 2.
Tracheostomy tubes (i) Portex tube with inner tube and obturator & (ii) Jackson's metal tracheostomy tube with inner tube and obturator.

dilator. The selection of the tracheostomy tubes either protex or metal depends on the indication for tracheostomy and the present clinical condition of the patient (**Figure 2**). All patients requiring prolonged ventilation, ICU stays with patient non responsive, anticipating need for positive pressure ventillation will require the cuffed portex tubes of proper size. In case of adult male patients its either 7.5 or 8 sized portex tube whereas in females its 7.5 or 7. However the Jackson's metal tracheostomy tube may be inserted in advanced laryngeal malignancy patients presenting with stridor where it is likely to be a permanent tracheostomy and patient requires to be sent home with the same after educating him and his relative on how to clean and use the inner tube. The requirement of suctioning can be avoided with cleaning by removing inner tube and reinserting it. However the metal tube can be an impediment in cases where there is bleeding with granulations around the stoma site, when an MRI is required etc. The selection of tracheostomy tube of appropriate size is important. Usually in intubated patients it is easy to ascertain the size but during emergency tracheostomy ensure that the tube with larger diameter is inserted so that chances of tube block in the early post operative period is minimized. Usually it's the cuffed portex tube that is used in adult patients with instructions to deflate the cuff at regular intervals. Now the portex tubes do come with the inner tube and hence is preferred over the metal tubes to avoid skin corrosion and granulations with better tolerability among patients. The maintenance of personal hygiene around the stoma site and cleaning of the tube must be explained well to avoid infection and stomal problems.

5. Salient features of a few of the challenges during tracheostomy

i. ***Pediatric Tracheostomy*** – This is definitely a challenging area considering the tracheostomy technique. It was primarily indicated for inflammatory diseases (epiglottitis, abscesses or laryngotracheobronchitis) or trauma prior to early 1960s. At present, almost two-thirds of pediatric tracheostomies are performed

in infants less than 1 year of age, the main indications been congenital or acquired laryngotracheal stenosis, prolonged ventilator support and regular pulmonary toileting for persistent aspiration in cases of pharyngotracheal discoordination. However severe anterior neck burns, vascular anomalies of lower neck and the need for high peak inspiratory pressures that may cause pnuemomediastinum/pnuemothorax are all contraindications to performing it.

Infant larynx is located at the levels of third to fourth cervical vertebra and it starts to descend by age of two to reach adult levels. The challenges in an infant larynx are based on its anatomy wherein up to ten tracheal rings lie in the neck in infants, it's one-third the size of adult larynx and thyroid notch lie behind the hyoid bone. The technical difficulties in performing a peadiatric tracheostomy is mainly due to the pliable cartilages of infant trachea which can make it difficult to identify from other tubular structures in the neck, thus increasing the possibility of injuring the major structures nearby like recurrent laryngeal nerve, esophagus etc. For peadiatric tracheostomies most palpable landmark is cricoid cartilage, unlike thyroid notch in adults. The location of tracheotomy in children for aspiration or prolonged ventilator support, is made at third or fourth tracheal rings. When indicated for incipient laryngotracheal stenosis (LTS) due to prolonged intubation, it must be at first tracheal ring to preserve as many normal tracheal rings distally as possible or low in the neck at sixth or seventh tracheal rings so as to spare sufficient number of normal rings between the stenosis and tracheostoma. The surgery is performed under general anesthesia with the airway secured where ever possible with an endotracheal tube or a rigid ventilating broncoscope. For cosmetic reasons a small horizontal incision is preferred which is then deepened through subcutaneous fat plane to strap muscles and bipolar diathermy used to cauterize small vessels in the surgical field. The anterior surface of trachea is exposed over 3 to 4 tracheal rings. The debate is still ongoing whether a vertical or horizontal tracheal incision, with or without flap should be made. However the vertical incision seems safer and preferred during all the procedures done at our institute. However tracheal stay sutures are placed or either sides and secured to either sides of chest or an inferiorly based Bjork flap transecting a single tracheal ring maybe taken and sutured to the inferior edge of skin to facilitate reinsertion of the tracheostomy tube while it is being changed or during accidental extubation. In infants accidental dislodgement of the tracheostomy tube is something that one must be careful about and hence the immediate post tracheostomy period is important with the infant requiring utmost care if possible by staff trained to do so. The smallest tracheostomy tube that ensures specifically adapted gas exchange in relation to child's age is selected. The postion of distal tip of tracheostomy tube, which should rest at least two to three rings above the carina, must be ensured hence the availability of appropriate sized tracheostomy tubes for infants is important. One ring Bjork flap is one of the ways to prevent anterior accidental subcutaneous dislodgement of the cannula.

ii. *Percutaneous Dilatational tracheostomy (PDT)* - The improvement in technique with adoption of percutaneous tracheostomy in the ICU patients has further revolutionized the procedure. Percutaneous dilatational tracheostomy (PDT) over a guidewire was invented by Ciaglia in 1985. This procedure has gained popularity owing to the easy execution of the same at the patients' bedside

S No.	Absolute contraindications	Relative contraindications
1	Inability to extend neck (Post trauma or otherwise)	Obesity
2	Severe Coagulopathy	Limited neck mobility
3	Infection on the neck wall	Distorted anatomy of neck
4		Previous neck surgeries
5		High ventilator support
6		Bleeding diathesis
7		Hypotension

Table 1.
Contraindications of percutaneous tracheostomy.

avoiding unnecessary and at times high risk transfers to the operation theaters and due to the cost- effectiveness. A recent meta-analysis of Putensen *et al*. in 2014 included 14 RCTs with 973 patients and found PDT to be associated with less incidence of stomal inflammation and infection but higher incidence of technical difficulties when compared to the conventional surgical tracheostomy [4]. This procedure as an emergency intervention requires an experienced surgeon and at any moment of time if required one must be prepared to convert to open procedure. There are definite contraindications as shown in **Table 1** which makes the patient selection process crucial. Proper patient selection and the wide use of ultrasound or bronchoscope can decrease failure rates and complications [5]. Though there are various techniques one should stick to the technique with maximum individual comfort as there is no evidence of superiority among various techniques.

6. Conclusion

Tracheostomy is a procedure that has revolutionized recovery of critically ill patients especially those requiring prolonged ventilation. The knowledge of likely difficulties is essential to be able to circumvent them and provide a secure airway as early as possible. It is only in patients who cannot be intubated or in whom it is difficult to intubate that this procedure becomes valuable. The advances in technology and procedures have made intubation possible in almost all patients though it calls for need of expertise and right equipments. Tracheostomy has its challenges in indications, timing, procedure and post procedural care. After the mentioned five periods we are probably into the, "***period of challenges***" wherein the possibility of tackling the encountered difficulties is being dealt with. It is the beginning of the journey as we move over the uncharted sea and this is an attempt to highlight a few common difficulties encountered.

A case report below highlights one such challenging situation likely during an emergency tracheostomy. The importance of early recognition and timely meticulous management can help avoid serious complications and morbidity. The foresight to secure an airway, as intubation was not possible and avoid an incision and drainage helped diagnose a pseudoaneurysm. Pseudoaneurysms of the internal carotid artery (ICA) are rare and harbor potential risk of life threatening hemorrhage.

7. Case presentation

History – A 62 year old lady with right side neck swelling having stridor was referred to our hospital. The patient a known diabetic, hypertensive with coronary artery disease was on medications for past 10 years. She gave history of dental pain with fever 10 days ago for which she consulted a doctor and was given medications. The fever and pain subsided but she developed a gradually progressive neck swelling on the right side with breathlessness that progressed to noisy breathing. She did not give history of blunt or penetrating neck injuries, voice change or dysphagia.

Examination – The patient had inspiratory stridor. Neck examination revealed a 5 cm x 3 cm firm to hard, tender swelling on the right side extending from just above the supraclavicular region to 1 cm lateral to the thyroid cartilage, laterally reaching upto the posterior border of the sternocleidomastoid. The examination of the oral cavity and oropharynx were unremarkable except for a carious right lower premolar tooth. On direct laryngoscopy the laryngeal inlet was found obstructed by a smooth bulge obstructing the glottis. The other clinical examination was found to be normal.

Investigations & treatment – The blood investigations were all within normal limits except for a raised total WBC count with neutrophilia. The primary concern was to secure an airway and hence an emergency tracheostomy was mandatory. The patient was shifted immediately to the operation theater and under local anesthesia tracheostomy was done. During the procedure after retracting the strap muscles the thyroid gland was found to be pushed by an unusually large mass on the right side. An attempt to retract or hook was futile with bleeding from the surface of the mass. The possibility of a vascular lesion in the region of the carotid sheath was suspected and hence meticulous and careful dissection was carried out to separate the mass. The thyroid gland was retracted medially and the mass held laterally for the visualization of the trachea. After confirming the position of the trachea the stoma was made between the third and fourth tracheal rings and 7.5 portex tracheostomy tube was introduced. The patient was comfortable post procedure and stridor relieved. USG neck was done which reported the possibility of a right internal carotid artery (ICA) pseudoaneurysm with a heteroechoeic collection compressing the right internal jugular vein (IJV). A CT angiogram was done which showed two pseudoaneurysms involving the right ICA with a peripherally enhancing hyperdense collection noted in the right carotid space surrounding the ICA and the distal common carotid artery, possibly a hematoma (**Figure 3**). Saccular pseudoaneurysms measuring 0.6 & 0.7 cm respectively causing complete airway compromise at C5 vertebral body level were noted (**Figure 4**). The opinion of the cardiovascular and thoracic surgeon was sought and endovascular stenting was advised as the definitive treatment option.

This case highlights one of the many challenges likely to be encountered during a tracheostomy especially when it is required to be performed as an emergency. "The eyes see what the mind knows" therefore awareness of this possibility helps the surgeon to be better prepared and avoid an on table catastrophe. The rupture of the pseudoaneurysm during the procedure can be life threatening and meticulous dissection can help avert an unusual adversity.

Discussion- The earliest known references to tracheostomy are made in the Rigveda published around 2000 BC. The term 'tracheotomy' was first published in 1649 by Thomas Fienus, and referred to the creation of an opening into the anterior tracheal wall to secure the airway. However, in 100 BC, Asclepiades of Bithynia was noted to be the first surgeon to perform an elective tracheotomy, but

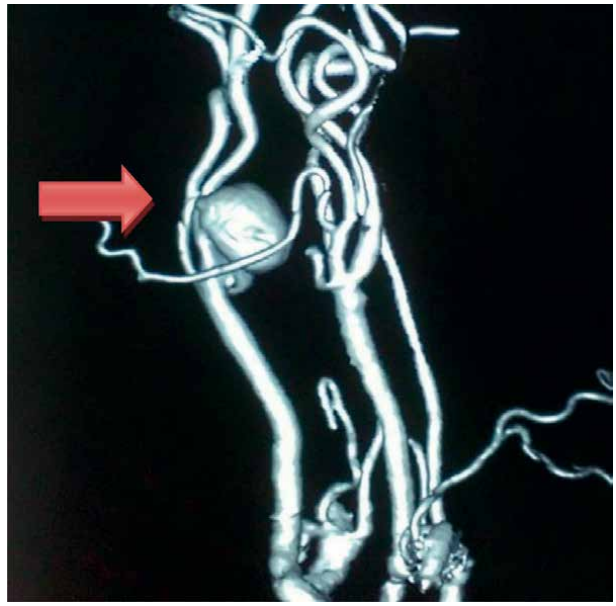

Figure 3.
CT angiogram showing pseudoaneurysms involving right ICA.

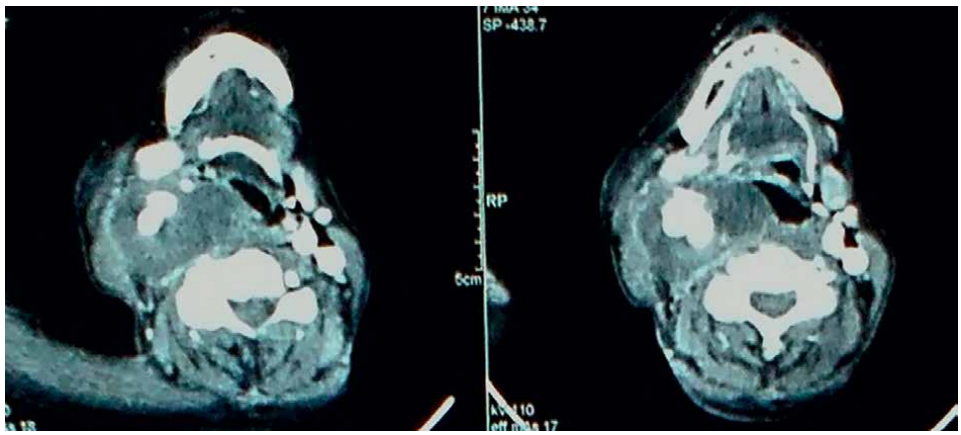

Figure 4.
CECT scan showing airway compromise due to the pseudoaneurysm (Rt).

the first documented successful case dates back to 1546 and is accredited to Antonio Musa Brassavola, as the patient was thought to have an 'abscess of the windpipe'. Traditionally, the use of a tracheotomy was reserved for cases of airway obstruction [5]. The evolution of tracheostomy can be divided into five stages; the period of legend, fear, dramatization, enthusiasm and rationalization. In the early 19th century, tracheotomy was employed in the treatment of diphtheria and other infectious causes which lead to airway obstruction. In the 1930s, tracheotomy was performed in patients with bulbar poliomyelitis to facilitate access to the airway for the removal of secretions [6]. In the late 1940s to the early 1950s, many began trialing the application of positive pressure ventilation through a tracheotomy [7]. Also, in the 1950s, this

surgical procedure was extended to multiple neurologic disorders including coma, brain tumors, multiple sclerosis, and so on. The growing use of tracheostomy led it to be considered as a routine procedure that was both effective and relatively safe, which sharply contrasts much of the previous thought equating tracheotomy to a 'pronouncing sentence of death' [8].

Special patient populations may benefit from early tracheostomy, including (1) high likelihood of prolonged mechanical ventilation (ARDS, COPD, failed primary extubation), (2) spinal cord injury and chronic neurologic disorders, and (3) traumatic brain injury patients and other patients with need for airways [9]. The operative technique of tracheostomy was refined by Chevalier Jackson. Studies have reported morbidity of 4–10% and mortality of less than 1% [10]. Though we have come a long way, the procedure is still with some hurdles. One such problem faced is that of an Internal Carotid artery (ICA) pseudoaneurysm which can make the procedure challenging. Pseudoaneurysms of the ICA are generally caused by trauma, with at least part of the aneurysm wall composed only of the adventitial layer or just by hematoma. It has a variety of causes including inflammation, trauma and various iatrogenic causes [11]. The age of presentation usually varies between 16 and 68 years. It may be asymptomatic and detected incidentally. Symptomatic pseudoaneurysms manifest with local or systemic signs and symptoms. Local effects of pseudoaneurysm (whether it is infected or not) are secondary to mass effect on adjacent structures causing compromise of function. This condition may manifest as a palpable thrill, audible bruit or pulsatile mass. Ischemia of the surrounding tissues due to vascular compromise may lead to necrosis of the overlying skin and subcutaneous tissues. Neurologic symptoms may develop secondary to nerve compression or ischemia. The compression of the adjacent vein may lead to edema and deep vein thrombosis. Thromboembolism is also a potential complication. The pseudoaneurysm may rupture leading to hemorrhage with its potential clinical sequel of life threatening shock. Pseudoaneurysm and deep neck space infection both present with posterior pharyngeal wall swelling, drooling, neck lump, hoarse voice or stridor. Clinically difficult to differentiate imaging modalities are required for the same. Investigations aiding in the diagnosis of pseudoaneurysm include Color Doppler sonography, contrast-enhanced CT (CECT), or MRI, and cervical angiography. Color Doppler shows swirling of blood flow within the pseudoaneurysm with a communicating channel to the parent artery (Yin Yang phenomenon) [12]. Ultrasonography (USG) is a valuable diagnostic tool for the detection of pseudoaneurysm. This modality is portable, readily available, inexpensive, fast, involving no ionizing radiations or renal toxic contrast material and non invasive. However it has limitations in assessing pseudoaneurysms of the deep arteries, moreover evaluations of vessels in fracture and hematoma may be difficult. Gray scale USG demonstrates hypoechoeic cystic structure adjacent to a supplying artery. CT angiography has advantage over other imaging modalities as it is not much operator dependant and has shorter acquisition time (<1 minute). Three dimensional CT angiography allows visualization of the lesion from all angles. It has high sensitivity and specificity in detecting arterial injuries. The MRI appearance of this lesion will vary depending on their size, age, extent of thrombosis and presence or absence of arterial occlusions. It shows flow void in a patent aneurysm and variable signal intensity in a thrombosed aneurysm [13]. A pseudoaneurysm generally appears on sectional MR images as small mass lesion that is closely contiguous with the patent artery but which projects outside its normal confines. The various treatment options for pseudoaneurysms include USG-guided compression, percutaneous thrombin injection, coil embolization, endovascular stent graft insertion, and surgery [14]. Lately, endovascular management

has proven to be advantageous over surgical management. It is less invasive and is helpful especially when surgery is contraindicated due to various reasons [15]. It also reduces hospital stay, and has eliminated the need for surgical procedures under general anesthesia. The case discussed here is of pseudoaneurysm masquerading itself as a neck abscess causing airway compromise. Our patient presented with a gradually progressive neck mass associated with fever without any history of recent trauma or surgeries. The clinical picture along with the raised total WBC count made us suspect a deep neck abscess. There are reported cases of pseudoaneurysms mimicking neck abscess. The mass effect caused by the pseudoaneurysm was to such an extent that the laryngeal inlet was not at all visualized depriving the possibility of airway restoration by endotracheal intubation. Therefore the need to resort to emergency tracheostomy. This report underlies the need to treat neck swellings with caution and emphasizes the fact that though tracheostomy has evolved over centuries it's not without any challenges even in expert hands.

Conclusion: Tracheostomy is a common critical care procedure performed by surgeons with the otorhinolaryngologist called in for management of patients in stridor or with a neck mass. In emergency setting the risk is even more and hence it is necessary to be aware of likely conditions that could result in a catastrophe. Pseudoaneurysm of the ICA is definitely one such possibility that must be kept in mind as it can mimic a neck abscess and fatal rupture into the airway can be catastrophic. The knowledge of such a possibility with meticulous dissection would be required to secure an airway following which patient may be investigated and definitive treatment provided.

Author details

Sapna S. Nambiar[1*], Slimcy Shylen[1] and Suma Radhakrishnan[2]

1 Government Medical College Kozhikode, India

2 Government Medical College Manjeri, India

*Address all correspondence to: snambiar25@gmail.com

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This book presents selected topics on the larynx and related problems, providing insight into recent advances in the field. Airway and speech are of critical importance in our daily lives and contribute to our personal well-being and safety as well as our communication with others. However, it is only when disease or injury impairs its function that we appreciate the relevance of the larynx. This book presents new clinical and research developments as well as future perspectives on airway-related problems and lesions. Chapters discuss laryngeal examination, laryngo-pharyngeal reflux, vocal cord paralysis, laryngeal leukoplakia, and much more.

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