Clinical and Surgical Management of Congenital and Iatrogenic Lesions of the Pediatric Larynx and Trachea

10

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Abbreviations

LM	laryngomalacia
SAL	synchronous airway lesion
SGS	subglottic stenosis
TM	tracheomalacia
TBM	tracheobronchomalacia

Introduction

This chapter reviews the pathology of some important congenital anomalies and acquired conditions of the larynx and trachea that may come to the attention of the pediatric head and neck surgeon and the pathologist. Numerous neoplastic diseases can afflict the larynx and trachea, but in general they are very rare in children. Primary benign neoplasms of the larynx and trachea include hemangioma, principally infantile hemangioma, granular cell tumor, and recurrent respiratory papillomatosis. Primary malignant neoplasms include rhabdomyosarcoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma [1, 2]. These and others have been discussed in other chapters: Chap. 13—Surgical Pathology of the Oral Cavity, Maxilla, and Mandible; Chap. 17—Surgical Pathology of the Salivary Glands; Chap. 23—Surgical Pathology of the Vascular system; and Chap. 31—Surgical Pathology of Pediatric Sarcomas of the Head and Neck. The specific microscopic, immunohistochemical, and genetic characteristics of those neoplastic diseases discussed in other chapters are not repeated in this chapter.

Surgical pathology specimens of congenital and iatrogenic laryngeal and tracheal lesions rarely come to the pathology laboratory. They usually consist of small cartilaginous and soft tissue fragments occasionally submitted during reconstructive surgery of the larynx or trachea. Most have minimal diagnostic significance. Granulation tissue, inflammatory polyps, cysts, and scar tissue related to intubation chronic airway injury and removed to treat airway obstruction may cause more diagnostic challenges to the pathologist, but these specimens also are uncommon, given the advances in interventional respiratory care in the current era [3, 4].

Laryngomalacia

Definition and Epidemiology

Laryngomalacia is abnormal softening of the cartilage and connective tissues of the larynx and is functionally characterized by inward collapse of laryngeal structures during inspiration [5]. It is the most common cause of stridor in neonates, responsible for up to 75% of cases [6–8]. However, the majority of infants diagnosed with laryngomalacia have a benign course, with 75–80% resolving stridor and related clinical symptoms between 12 and 36 months of age [9, 10]. Most cases present within the first 2 weeks after birth, but presentation may be delayed 4 or more months after birth [9, 11]. There is a slight male preponderance [12, 13]. Approximately 10% of cases develop severe accompanying symptoms such as failure to thrive, obstructive sleep apnea, gastroesophageal reflux or stridor-associated cyanosis, and of these more than half will require surgical intervention [7, 8, 14].

The pathogenesis of laryngomalacia is not resolved. Initial focus was on congenital abnormalities of laryngeal anatomy and cartilage development, but there has been no consensus that intrinsic cartilage abnormalities underlie laryngomalacia [15]. Subsequently, gastroesophageal reflux

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and neurologic disorders have been implicated, with the former being recognized as the most frequent comorbidity of laryngomalacia [16].

Synchronous airway lesions (SAL) are present in up to 50% of infants with laryngomalacia, and those with concomitant lesions tend to have more severe stridor and more often surgical intervention [5, 12, 17]. The most common SAL are subglottic stenosis and tracheomalacia, but include vocal cord paralysis, edema, and granulation tissue among other conditions [12, 17].

The majority of infants with laryngomalacia is treated with watchful conservative management, and only 5% to 15% require surgery [10, 13, 18, 19]. The most frequent surgical approach is an endoscopic supraglottoplasty, which involves a case-specific variety of mucosal arytenoid trimming and aryepiglottic fold division procedures [5, 20] Fig. 10.1. Less frequently, epiglottopexy or epiglottoplasty may be applied to mitigate posterior obstruction by the epiglottis, and tracheostomy may be required for unfeasible or failed endoscopic surgery [7, 14].

Classification

Multiple classification systems of laryngomalacia have been proposed, most based on static laryngoscopic observations of the epiglottis and larynx (see below), but some include dynamic studies as well [21]. The classification systems of McSwiney, Holinger, and Olney are noted; McSwiney et al. for first publishing a classification system for laryngomalacia, Holinger for presenting the most complete description of anatomical abnormalities, and Olney et al. for a simple, widely used classification [6, 9, 10, 21]. Recently, van der Heijden et al. proposed a classification based solely on observed dynamic airway findings using flexible fiberoptic endoscopy, arguing that anatomic abnormalities occurring during breathing have more relevance to clinical status than those abnormalities observed by rigid endoscopy during temporary interruption of ventilation [21].

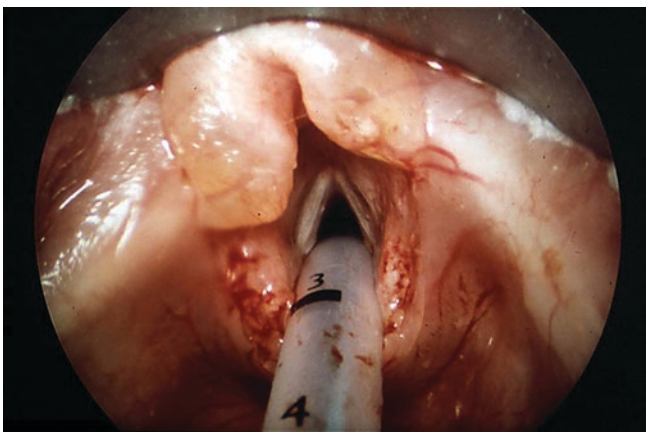

Fig. 10.1. Supraglottoplasty using "cold" microdissection technique showing division of short aryepiglottic folds and trimming of arytenoid mucosa. Endotracheal tube in situ

Macroscopic Features

The characteristic anatomic abnormalities of laryngomalacia as delineated by static and dynamic endoscopic findings are: an elongated and tubular epiglottis that deflects posteriorly on inspiration or collapses into the laryngeal inlet; foreshortened aryepiglottic folds that deflect medially; and excessive mucosa lining the arytenoid cartilages that deflects anteriorly [5]. Laryngeal mucosal edema is a frequent endoscopic finding, and other synchronous airway lesions such as subglottic cysts or tracheomalacia can be observed, however these may be hidden from a flexible fiberoptic laryngoscope [12] (Fig. 10.2).

Microscopic Features

Few histologic studies of laryngomalacia have been published. Chen and Holinger examined a postmortem series of whole mounted serially sectioned larynxes that included two cases with laryngomalacia, commenting on macroscopic details, but not employing microscopy [22]. Iyer et al. examined laryngeal mucosa from aryepiglottomy surgery focusing on inflammation related to gastroesophageal reflux [23]. Chandra et al. performed microscopy studies on tissues from supraglottoplasty, with the predominant findings of subepithelial edema and dilatation of subepithelial lymphatics. Mucosal and submucosal inflammation was minimal and no abnormality of included cuneiform cartilage was noted [15].

Immunohistochemical/Molecular Diagnostic Features

There is no specific immunohistochemical or genetic molecular diagnostic feature of laryngomalacia. Laryngomalacia occurs as an isolated condition, with multiple birth anomalies and as a component of numerous genetic syndromes such as Trisomy 21, and 22q11 deletion syndrome [24–26].

Differential Diagnosis

The differential diagnosis of laryngomalacia is that for inspiratory stridor and is a clinical and diagnostic imag-

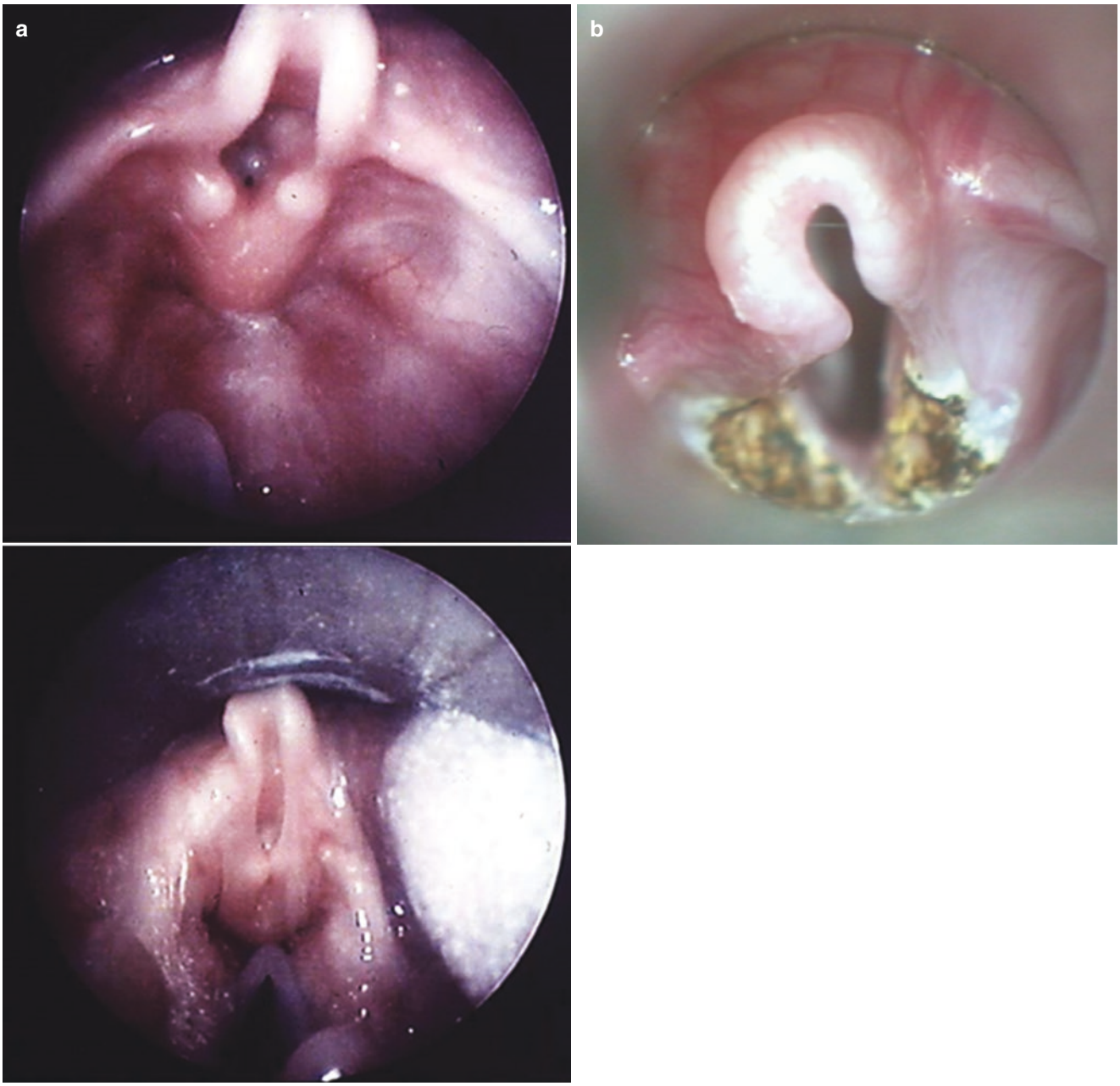

Fig. 10.2 (**a**) Typical appearance of severe laryngomalacia at endoscopy with elongated tubular shaped epiglottis, short aryepiglottic folds and redundancy of mucosa covering showing collapse and near-total airway obstruction on inspiration; (**b**) Appearance after supraglottoplasty using CO_2 laser

ing task. Although laryngomalacia is the most common cause of inspiratory stridor, the differential diagnosis includes a wide variety of lesions such as other congenital laryngeal disorders, laryngeal trauma, tracheal and bronchial abnormalities, upper airway obstructive lesions, and airway inflammatory conditions [6]. The definitive diagnosis of laryngomalacia is confirmed by laryngoscopy [22].

Congenital Laryngeal Stenosis

Definition and Epidemiology

Laryngeal stenosis is defined as an abnormal narrowing of the lumen of the larynx. The narrowing can involve the supraglottic or glottic areas of the larynx, but the subglottic region is most often the site of narrowing in neonates and

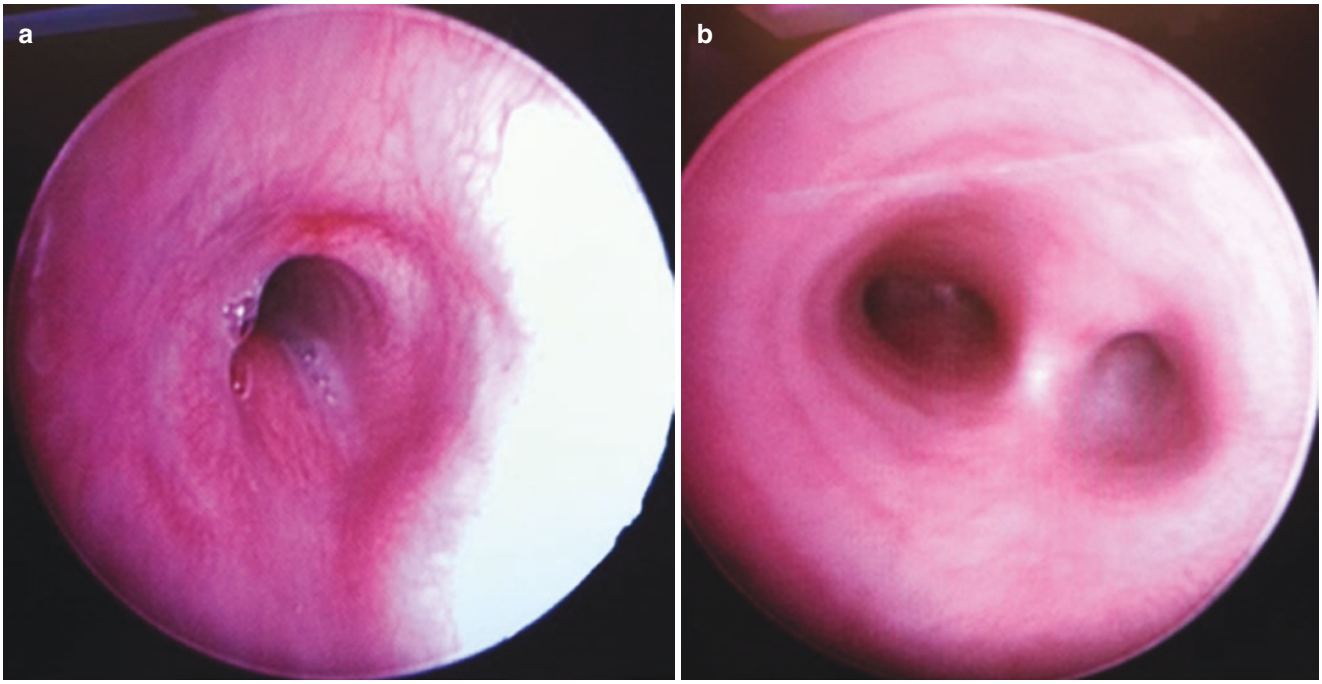

Fig. 10.3 (**a**) Neonate with subglottic stenosis secondary to a "trapped" tracheal ring; (**b**) Distal tracheal view of the neonate above showing synchronous lesion. In this case a tracheal or "pig" bronchus was detected shown at the 3 o'clock position. The right upper lobe bronchus originates from the trachea rather than the right main bronchus. This finding is typically misdiagnosed and labelled as a normal carina by the inexperienced bronchoscopist

children. The subglottic region extends from just below the vocal cords to the caudal end of the cricoid cartilage. Subglottic stenosis can be the consequence of a congenital abnormality of the larynx, an acquired injury or an idiopathic condition. The latter mainly occurs in Caucasian perimenopausal women and will not be further discussed [27]. Prior to the common use of endotracheal intubation in neonates and young children, congenital conditions that resulted from abnormalities in the development of the upper airway, although rare, were a significant cause of laryngeal stenosis and remained so through the 1960s and early 1970s [28]. In contrast, the acquired causes of laryngeal stenosis before the 1960s included diphtheria in the first few decades of the twentieth century and, later, trauma, until they were supplanted by complications of endotracheal intubation beginning in the 1970s [29]. Intubation-associated acquired laryngeal stenosis is discussed below. In the contemporary time, acquired causes account for approximately 95% of subglottic stenosis in children and congenital causes about 5% [30].

The narrowest part of the larynx in the newborn and young child is at the cricoid ring [31]. The accepted luminal diameter for diagnosis of subglottic stenosis in a full-term neonate is $\leq$ 4 mm (in a preterm newborn < 3 mm) [32]. Congenital subglottic stenosis results from failure of embryonic complete recanalization of the cricoid ring that also includes laryngeal webs and atresia, as a component of a syndrome or anatomical developmental abnormality of the head and neck or, rarely, as an isolated congenital deformation of the cricoid cartilage. The majority of congenital subglottic stenosis is not associated with other developmental defects [33] although rarely other causes of subglottic stenosis such as a "trapped" tracheal ring can present with synchronous lesions (Fig. 10.3a,b).

The most common syndrome associated with congenital subglottic stenosis is Down syndrome, with the airway including subglottis and trachea being smaller than those of other children, which incidentally also increases the vulnerability of the larynx to acquired subglottic stenosis [34]. Velocardiofacial syndrome (22qll.2 deletion syndrome) has multiple otolaryngologic abnormalities including subglottic stenosis that is often associated with glottic webs [25, 35] (Fig. 10.4).

The most common clinical presentation of congenital subglottic stenosis is stridor, usually biphasic and evident from birth. However, minor degrees of stenosis may delay clinical presentation for several months. Another important presentation is prolonged or recurrent croup-like symptoms. Subglottic stenosis is the third most common cause of congenital stridor, after laryngomalacia and vocal cord paralysis [28]. Of note, unlike acquired subglottic stenosis, the majority of mild or moderate congenital subglottic stenosis will

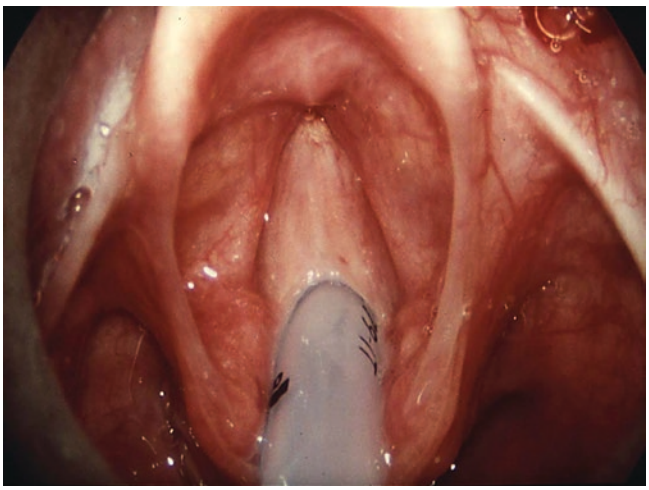

Fig. 10.4 Laryngeal glottic web with small endotracheal tube in situ. This neonate presented with stridor and a high-pitched weak cry

clinically resolve as the child grows. More severe degrees of stenosis present with acute airway obstruction at birth requiring tracheostomy or other urgent intervention.

Classification

Classification of congenital subglottic stenosis can be made on the basis of associations as mentioned above, location, extent, and, perhaps most clinically important, severity of stenosis. A widely accepted classification using the severity of stenosis is the Myer-Cotton grading scale [36]. This grades the stenosis by percentage of obstruction compared to expected normal for age luminal diameter as determined by the use of different size endotracheal tubes. Grade I is up to 50% obstruction, grade II 51% to 70%, grade III 71% to 99%, and grade IV total obstruction. The clinical significance of this grading system is that congenital subglottic stenosis of grades I or II generally resolve as the child grows and therefore can be conservatively managed while grade III usually requires surgical intervention, such as tracheostomy or reconstruction surgery. If not identified antenatally as congenital high airway obstruction syndrome (CHAOS) grade IV presents as acute airway obstruction at birth that requires urgent attention [37].

Histopathology Features

The diagnosis of subglottic stenosis is made by laryngotracheal endoscopy. The surgical pathologist may receive fragments of mucosa, submucosal soft tissue, and cartilage removed during cricotracheal resection or laryngeal reconstruction but generally without additional diagnostic significance. Whole mount sections of the postmortem larynx from children with subglottic stenosis can show normally shaped but small cricoid cartilage, abnormally shaped cricoid cartilage, submucosal fibrosis, excessive mucous glands, and "trapped first tracheal ring" correlating with the clinical diagnosis of subglottic stenosis [38].

Tracheomalacia

Definition and Epidemiology

Tracheomalacia (TM) is softening of the tracheal cartilage that results in excessive pliability and collapsibility of the trachea and is accompanied by increased width of the tracheal posterior membrane (pars membranacea) leading to various degrees of membrane redundancy. The consequence is apposition of the anterior and posterior walls of the trachea during breathing resulting in airway obstruction [39]. Clinical and pathological features divide tracheomalacia into two groups representing the standard classification: congenital (primary) and acquired (secondary) [40].

Congenital Tracheomalacia

Tracheomalacia is the most common congenital tracheal abnormality and the fourth most common congenital cause of stridor in children after laryngomalacia, vocal cord paralysis, and laryngeal stenosis (laryngeal webs and subglottic stenosis) [6, 41]. Of the few reports available, the incidence of congenital tracheomalacia ranges from 1:1445 to 1:2100 [42, 43]. Pediatric cohort studies have reported a male: female preponderance of congenital tracheomalacia ranging from 2:1 to 4:1 [44–46].

The majority of children with congenital tracheomalacia clinically present within the first 12 months after birth, most often within a few weeks and uncommonly at birth [40]. However, in Mair and Parsons' study of 38 infants with tracheobronchomalacia that includes a cohort of 12 with tracheomalacia alone all but two had symptoms from birth. The symptoms included among others chronic respiratory obstruction, cyanosis, stridor, and barking cough [44]. Of note, tracheomalacia most commonly is intrathoracic and tracheal collapse occurs during expiration, with stridor either expiratory or biphasic, while stridor with the less common extrathoracic tracheomalacia occurs during inspiration [40]. Severe congenital tracheomalacia causes significant airway obstruction and can be accompanied by apneic spells with potentially sudden death, although such spells more frequently are associated with cardiovascular causes of tracheomalacia (see below) [47]. Mitigation of severe symptoms may require prolonged endotracheal intubation, tracheos-

tomy, or urgent surgery [48]. Most children with mild or moderate congenital tracheomalacia improve over 1 to 2 years with appropriate attention to airway secretions and infection [46, 49].

Congenital tracheomalacia may be a solitary abnormality but more frequently it is associated with other developmental airway abnormalities, a large number of congenital syndromes or cartilage disorders [40]. The former includes laryngomalacia, bronchomalacia, subglottic stenosis and vocal cord paralysis. However, the most common association is with esophageal atresia-tracheoesophageal fistula [40]. Esophageal atresia-tracheoesophageal fistula distorts the normal anatomy of the trachea, widening the posterior membrane and reducing the curvature and the length of the tracheal cartilages [50] (Fig. 10.5a). The tracheomalacia consequent to the abnormal development of the trachea commonly persists to varying degrees after repair of the esophageal atresia and tracheoesophageal fistula [51]. Rarely treatment may be required such as aortopexy or even insertion of a tracheal stent (Fig. 10.5b), indicated only when other modalities of treatment fail.

Acquired Tracheomalacia

Acquired tracheomalacia is more common than congenital tracheomalacia [40]. It is defined as tracheomalacia resulting from injury to a previously normal trachea. Symptoms are similar to those of congenital tracheomalacia and can be present at birth or may be delayed in presentation. The causes differ from those associated with congenital tracheomalacia and include prematurity, sequelae of prolonged intubation and tracheostomy, traumatic injury, infections and, in particular, conditions or lesions that compress the trachea: aberrant thoracic vasculature, enlarged left atrium of the heart, abnormalities of the spine and sternum and extrinsic neoplasms [48]. Of the extrinsic compressive causes, abnormalities of the thoracic vasculature and heart are the most common in children [7]. The cardiovascular anomalies include double aortic arch, anomalous innominate artery, right aortic arch, aberrant right subclavian artery, and pulmonary artery sling [40, 52, 53]. Symptoms of cardiovascular compression of the trachea often present at or within the first few weeks of birth, although rarely clinical presentation can be absent until adulthood [52].

Diagnosis and Treatment

The diagnosis of tracheomalacia encompasses clinical symptoms and signs, a wide variety of diagnostic imaging techniques from plain radiographs to multidetector computed tomography, fluoroscopy, pulmonary function testing, and others. However, bronchoscopy remains the "gold standard." These and other diagnostic modalities are reviewed in several papers [40, 48, 54, 55].

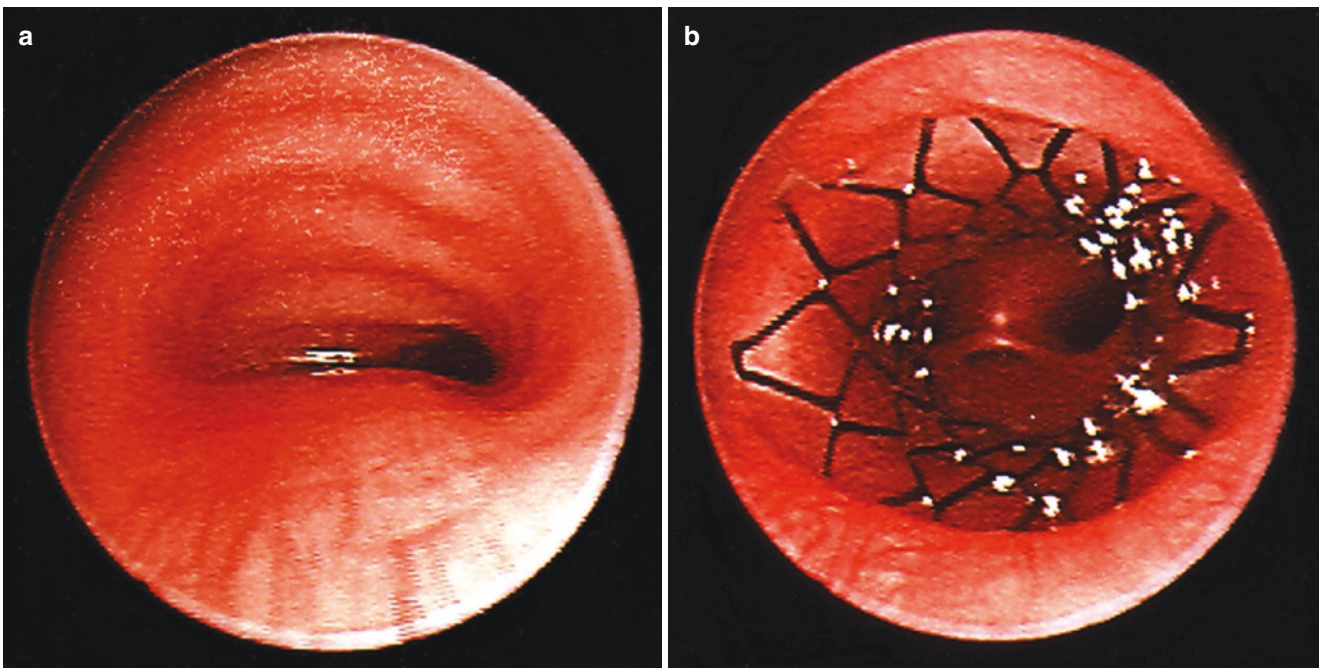

Fig. 10.5 (**a**) Child with severe tracheomalacia as a result of a tracheoesophageal fistula (TEF). Note the widening of the posterior membranous trachea and a flattening of the normal anterior curvature of the tracheal cartilage. (**b**) Distal TEF can be seen after deployment of a stent

Austin and Ali divided the treatment of moderate to severe tracheomalacia into five modalities: (1) long-term ventilation/CPAP/tracheostomy; (2) resection of involved segment; (3) external splinting; (4) pexy procedures such as tracheopexy or aortopexy; and (5) stenting [54]. As mentioned above, the treatment for the majority of children with mild tracheomalacia is the conservative approach of watchful waiting for the usual improvement of tracheomalacia over time. Tracheostomy and long-term ventilation have been superseded to a degree by more modern treatments in part because they have been associated with exacerbating tracheomalacia [49]. Resection of affected segments of the trachea is confined to segments that are short enough to allow end-to-end or slide tracheoplasty, generally less than 30% of the length of the trachea segments. However, these short lengths of tracheomalacia occur in a minority of children [48, 56]. Aortopexy and other pexy procedures have been surgical standards of tracheomalacia treatment for over 30 years [48, 57, 58]. This is done by thoracotomy or thoracoscopy and involves lifting the aorta or other compressing vessels away from the trachea and fixing them to the sternum or other structures to relieve the extrinsic compression. External splinting with prosthetic materials may be used when the extent of the tracheomalacia is likely to exceed that satisfactorily mitigated by aortopexy [48]. Metal stents have been endoscopically inserted into the trachea as an alternative to extrinsic splinting, but this has complications such as recurrent airway obstruction from granulation tissue formation and fibrosis and difficulties in replacing stents when the patient outgrows the stent [59].

Pathology Features

The surgical pathologist infrequently is presented with tissue related to surgical treatment of pediatric tracheomalacia. This material may consist of fragments of tracheal cartilage, posterior membrane, granulation tissue, or fibrous tissue. In the very rare instance of a segmental excision of tracheomalacia the pathologist may have opportunity to examine cross-sections of trachea. Postmortem whole mount cross-sections were studied by Wailoo and Emery from children with respiratory diseases and in a separate study from children that had tracheoesophageal fistulas [50, 60]. These were primarily morphometric studies, but some comments regarding histology were presented. The 1980 study from children with respiratory diseases had a cohort that had no congenital disease but had histories of respiratory symptoms. This suggests that some of the cohort may have had tracheomalacia [40]. The main findings were increased width of the posterior membrane and increased perimeter of the cartilage. The tracheas of children that had tracheoesophageal fistulas showed, distal to as well as around the fistula, deficiency of cartilage and increase in the posterior membrane length resulting in a laterally wide and anteroposterior flat trachea.

Immunohistochemical/Molecular Diagnostic Features

There are no specific immunohistochemical or molecular genetic markers for tracheomalacia. Numerous genetic syndromes have tracheomalacia as a component of their disorder [40, 48].

Differential Diagnosis

The symptoms of tracheomalacia are typical but not specific. Many conditions enter into the differential diagnosis of tracheomalacia and must be excluded by appropriate clinical, diagnostic imaging, and bronchoscopic examinations. These include asthma, respiratory tract infection, foreign body aspiration, hypertrophied tonsils and adenoids, airway cysts, and for extrathoracic tracheomalacia, congenital laryngeal abnormalities [6, 46].

Congenital Tracheal Stenosis

Definition and Epidemiology

Congenital tracheal stenosis is a rare developmental abnormality characterized by significantly narrowed tracheal lumen within complete tracheal cartilage rings (Figs. 10.6 and 10.7). Affected segments of the trachea can occur anywhere along the trachea, segments vary in length, multiple segments may be present, and the developmental abnormality can extend into bronchi. Long segment congenital tracheal stenosis, defined as narrowing of > 50% over the length of the trachea, presents the severest clinical consequences and the greatest treatment challenge. The incidence is estimated to be 1:64,500 live births [61]. Males are more affected than females [62]. Cardiovascular disease accompanies congenital tracheal stenosis in approximately 2/3rds of cases, with left pulmonary artery sling being the most common specific anomaly [62, 63] (Fig. 10.8). Extra-cardiovascular associations are aberrations of right lung upper lobe (Fig. 10.9), carinal trifurcation, and single lungs [64].

Classification

A simple classification of congenital tracheal stenosis is "long segment" (> 50% of the length of the trachea) and "short segment" [64]. Cantrell and Guild presented a now

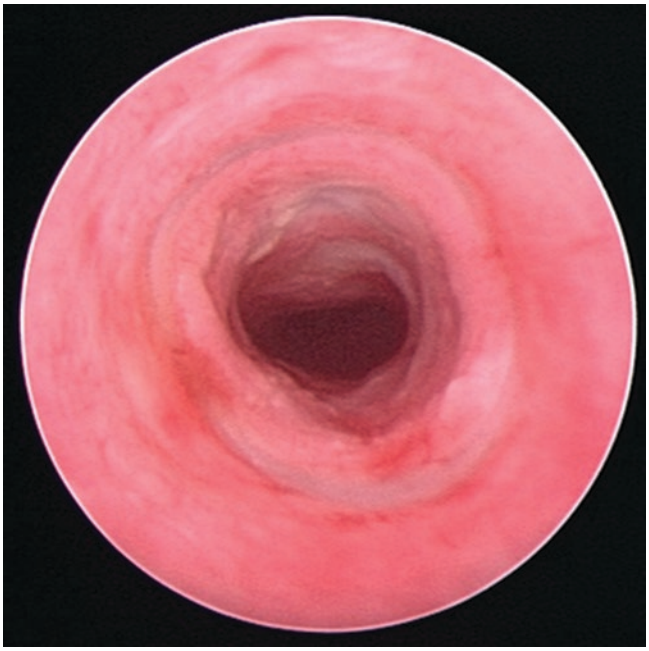

Fig. 10.6 Typical appearance of mid-tracheal stenosis showing complete tracheal rings

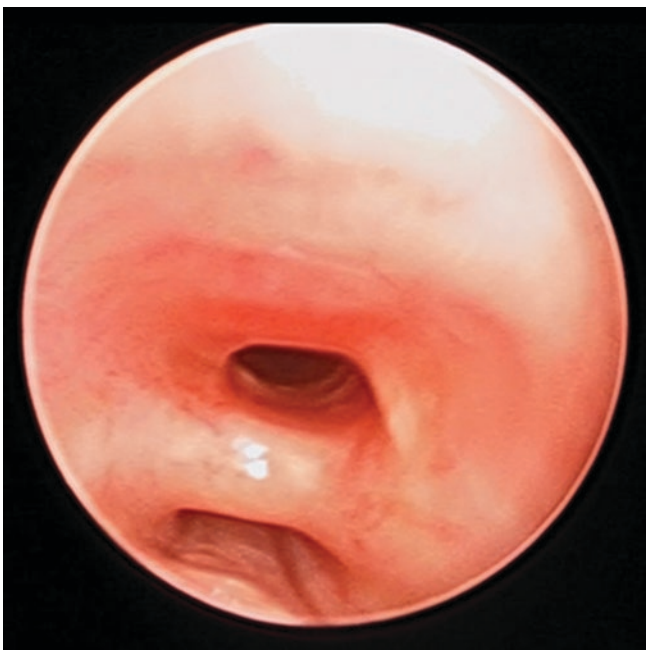

Fig. 10.7 This endoscopic photo shows a TEF posteriorly and tracheal stenosis anteriorly starting at the take-off of the TEF

widely used morphologic classification that has three types of tracheal stenosis: (1) generalized hypoplasia with total tracheal involvement; (2) funnel-like stenosis tapering cranially to caudally; and (3) short segment (2–5 cm length) [61, 65].

Symptoms and Diagnosis

Symptoms of tracheal stenosis become evident when the tracheal lumen is narrowed by at least 50%. They include biphasic or expiratory stridor, respiratory distress, apneic spells and cyanosis, depending on the age of the individual and the severity of the stenosis [66]. In most studies, the majority of infants have moderate to severe tracheal stenosis and, especially with concomitant cardiovascular disease, present at birth. However, lesser degrees of airway obstruction may delay symptoms for months. Although various diagnostic imaging modalities are used in the diagnosis of tracheal stenosis rigid bronchoscopy remains the "gold standard" for identifying ring cartilages and tracheal stenosis and consequently for the definitive diagnosis of congenital tracheal stenosis [61].

Treatment

It is estimated that approximately 10% of children with tracheal stenosis can be managed conservatively without surgery [67, 68]. However, this does not take into account what is presumed to be an undiagnosed cohort of children who have not presented for medical intervention. Cheng et al. have suggested that children who have all three of minor or no symptoms, absence of short segment involvement, and no area of tracheal stenosis greater than 40% of the age-related normal tracheal luminal diameter may be conservatively treated for the stenosis, although any significant associated cardiovascular abnormalities would require appropriate management [62]. Generally, children with tracheal stenosis that have moderate to severe airway obstruction will require surgery. The procedures include endoscopic dilatation, tracheoplasty with autologous or synthetic patches, tracheal resection with end-to-end anastomosis, and the "gold standard" of slide tracheoplasty [62, 67, 69, 70]. Correction of associated cardiovascular or other associated conditions is part of the management of congenital tracheal stenosis. Postsurgical complications to the tracheal repair include development of granulation tissue at the anastomoses and tracheomalacia related to the segmental devascularization of the trachea during slide tracheoplasty [61, 67]. These complications may require repeated balloon dilation or stenting of the affected region. The mortality of surgical correction of congenital tracheal stenosis depends greatly on associated cardiovascular abnormalities. With a cardiac abnormality that of itself requires surgical intervention, the mortality of tracheal stenosis surgery has been approximately 70% [61]. Reports on combined short and long-term mortality of tracheal stenosis surgery not associated with a cardiac abnormality vary greatly, averaging about 25%, although more recent reports have mortality reduced to about 10% [61, 64, 67, 70].

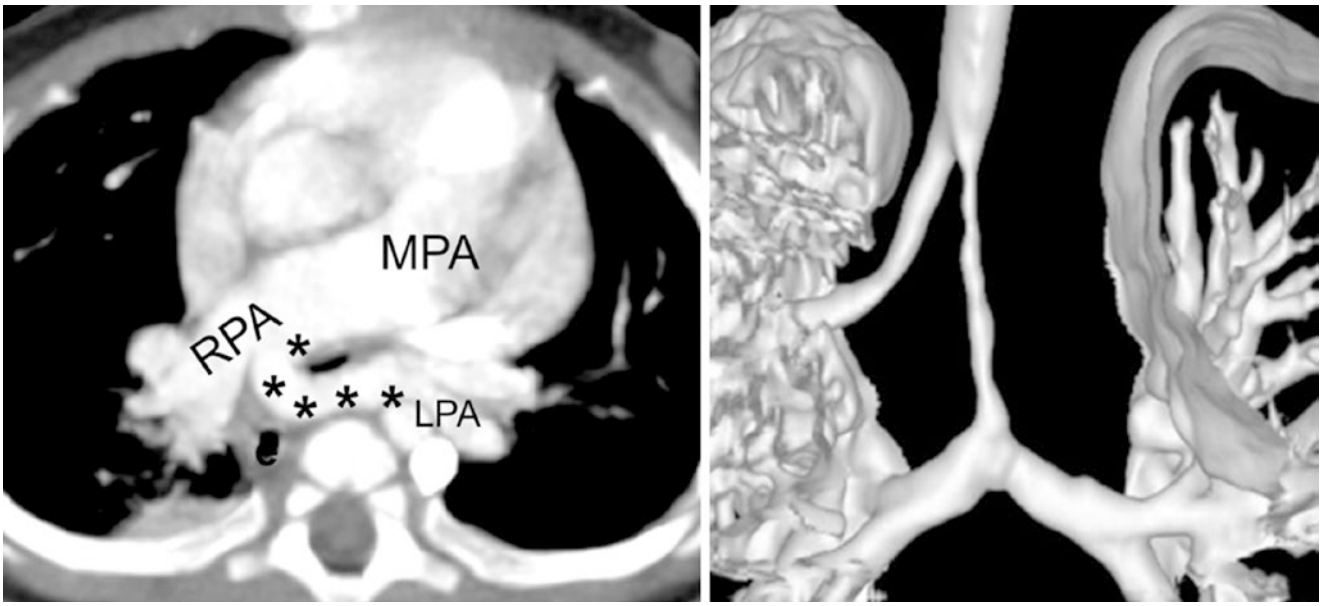

Fig. 10.8 MR of child with congenital long-segment tracheal stenosis (coronal view shown on right) and an associated cardiac vascular anomaly (axial view on left). The left pulmonary artery (LPA) which under normal anatomical conditions originate from the main pulmonary artery (MPA) instead derives from the right pulmonary artery (RPA) and creates a pulmonary "sling" posterior to the narrowed tracheal segment

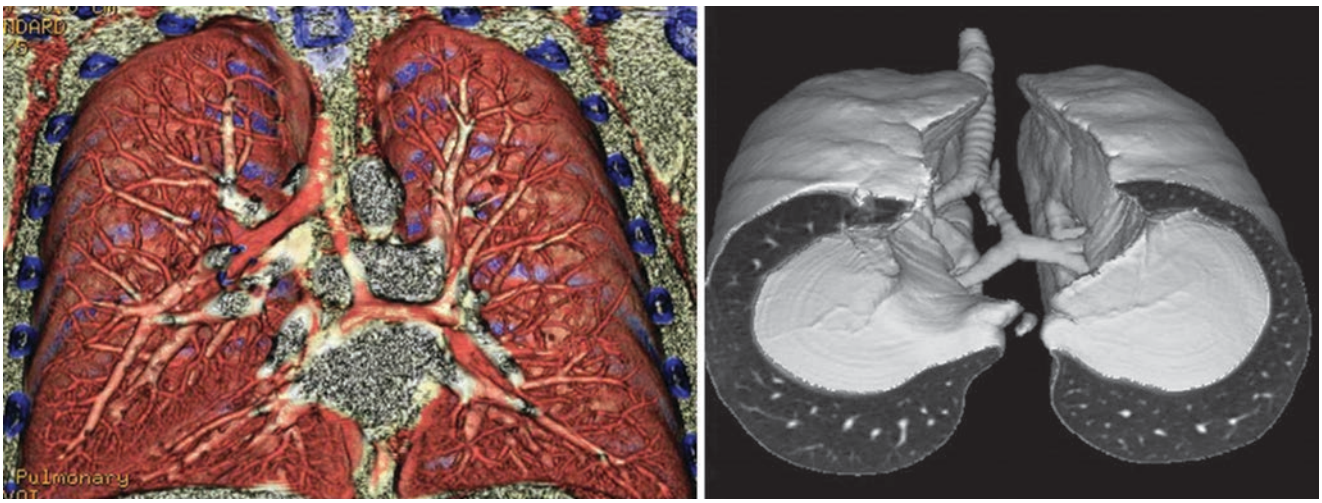

Fig. 10.9 MR colored 3-D reconstruction of a "bridging bronchus," which is composed of complete tracheal rings. This anomaly can easily confuse the inexperienced bronchoscopist mistaking the upper bifurcation as the primary carina

Endotracheal Intubation-Associated Pathology of the Larynx and Trachea

Definition and Epidemiology

Endotracheal intubation of children began to be accepted in the 1940s, but not without concerns and cautions [71, 72]. Over the ensuing seven decades, pediatric endotracheal intubation, even for preterm neonates, has become a common, generally safe, and often lifesaving procedure. However, even in the modern age complications affecting the larynx and trachea arise. These are, fortunately, infrequent consequences of intubation and include serious acute and long-term injuries and conditions such as laryngeal and tracheal perforation and fatal mucus and blood airway plugs that generally are not in the purview of the surgical pathologist [73–

75]. The surgical pathologist's contribution to the management of endoscopic laryngotracheal injury is limited, but may involve diagnosis or confirmation of mucosal ulceration, necrosis or metaplasia, stenosing airway fibrosis, reactive inflammatory granulomata, subglottic cysts, and unexpected synchronous airway lesions (see below).

The factors associated with laryngotracheal intubation injury include the size and age of the neonate or child, the size of the endotracheal tube, the type and size of the tube cuff if used, the duration of intubation, the skill and experience of the operator performing the pediatric intubation and the intrinsic anatomy of the larynx especially as related to abnormalities of head and neck development [4, 76]. A particular anatomic factor of the child's larynx is that the cricoid ring, unlike that in the adolescent or adult, is narrower than the glottis until the child reaches approximately 8 years of age [31].

Classification

Few classifications have been applied specifically to the histopathology of intubation-related upper airway injuries in children, with most classifications focusing on clinical aspects or risk factors. Blanc and Tremblay in 1974 presented a classification divided into three periods: the early or immediate complication period related to insertion of the tube, the period of injuries occurring while the tube is in place, and the period of injuries related to extubation [77]. Benjamin based a classification on the severity of lesions—mild, moderate, and severe—determined by a combination of: clinical factors contributing to laryngeal intubation trauma; endoscopic evaluation of the type and severity of lesions; and assessment of photographic images obtained during laryngoscopy [78] (Figs. 10.10 and 10.11). Histopathology studies of pediatric airway intubation-associated injuries have used postmortem specimens and mainly focused on the time course of the lesions typically progressing from mucosal necrosis and ulceration through laryngeal and tracheal fibrous stenosis (see below) [79].

Pathology of Selective Intubation-Associated Lesions

Mucosal Edema: The most common intubation-associated injury of the larynx and trachea is mucosal edema, occurring in almost all that receive airway intubation. This generally resolves within hours or a few days, but can present as acute postextubation airway obstruction, especially with involvement of the narrow subglottis of a young child [71, 77]. Except for extraordinary circumstances, the surgical pathologist will not be presented with a specimen sample of laryngotracheal mucosal edema.

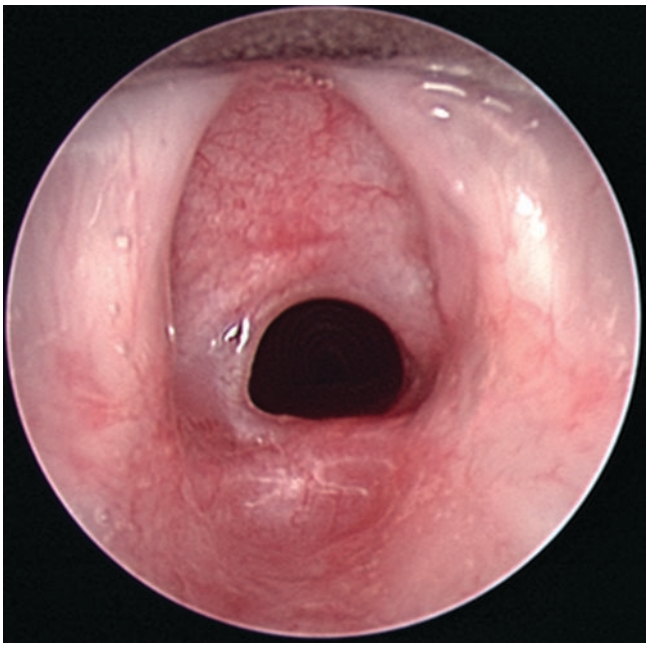

Fig. 10.10 Laryngeal photography can be used to document and to stage the degree of stenosis. In this photo, a moderate well-formed acquired subglottic stenosis can be seen This followed prolonged intubation in the neonatal period

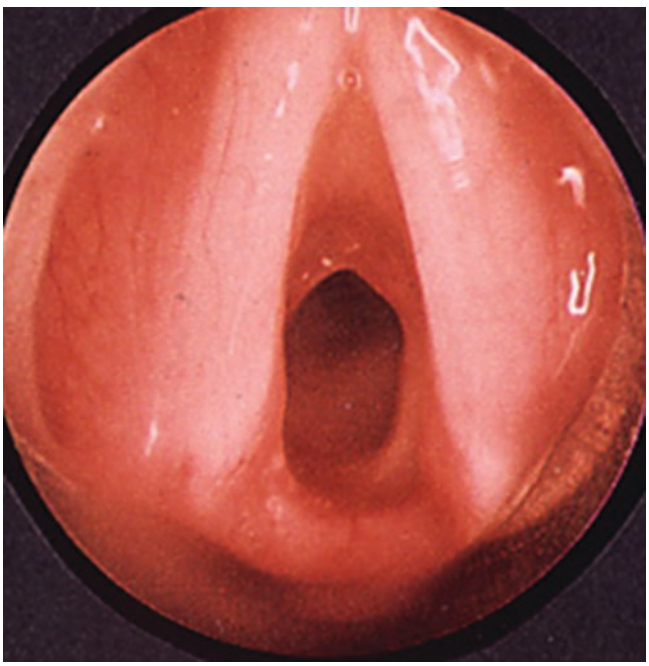

Fig. 10.11 An "early" stenosis is developing in the subglottic region following prolonged intubation

Mucosal Necrosis and Ulceration: Mucosal ulceration also is a nearly universal consequence of airway intubation in infants and children due to the vulnerability of the mucosa to ischemia from cuff-inflation capillary compression and to mechanical injury from the intubation tube caused by move-

ment of the head and neck of the child during intubation [78–80]. Ulceration occurs with varying intensity, usually, but not necessarily, related to the duration of intubation [79, 81] (Figs. 10.12 and 10.13).

However, in the majority spontaneous resolution of the laryngeal ulceration follows the discontinuation of intubation, with only a minority having serious or long-term sequelae [81, 82]. Several studies of the histology of the larynx and upper trachea in children that have undergone laryngotracheal intubation have confirmed a standard sequence of injury and healing [79, 81–84]. The sequence is similar for the studies done in different time periods including the more contemporary ones. The studies have been based on postmortem specimens and mostly involved infants, although some included older children of various ages. The standard sequence begins with mucosal necrosis leading to ulceration within a few hours of intubation. The necrosis primarily relates to mucosal capillary compression from the intubation tube with consequent mucosal ischemia and from potential friction-related mechanical injury from insertion of the tube or tube movement from manipulation of the head and neck of the patient [85]. In general, the extent and severity of the mucosal necrosis and ulceration relates to the duration of intubation. The most significantly affected areas in the larynx are the posterior glottis and cricoid ring. More severe mucosal injury is accompanied by ulceration and chondritis of the arytenoid and cricoid cartilages and can extend into the upper trachea, but these complications often require several days to develop (Fig. 10.14).

The second phase of the sequence is reparative activity that begins 4 or 5 days after the onset of injury. This occurs even with intubation continuing and consequently injury progressing. The healing consists of development of squamous metaplasia, formation of granulation tissue, and varying degrees of fibroblastic proliferation. The granulation tissue can become polypoid and potentially cause airway obstruction, particularly when located in the glottis or subglottis (see Chap. 11) [73, 86]. The third phase is the devel-

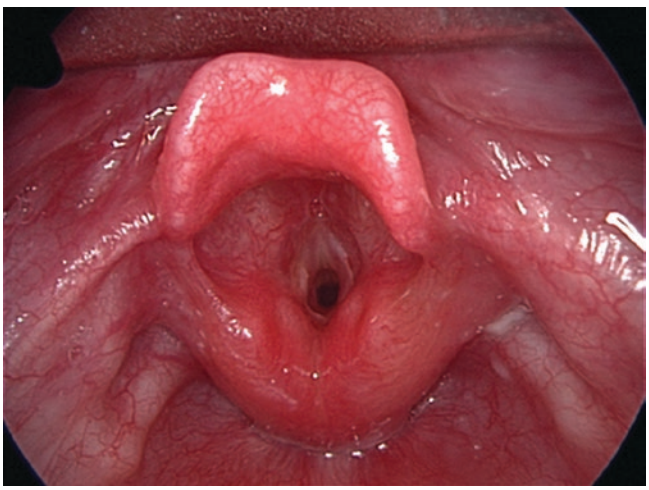

Fig. 10.12 Significant transglottic inflammation and mucosal ulceration can be the result of prolonged intubation as seen in this endoscopic photo taken immediately after removal of the endotracheal tube

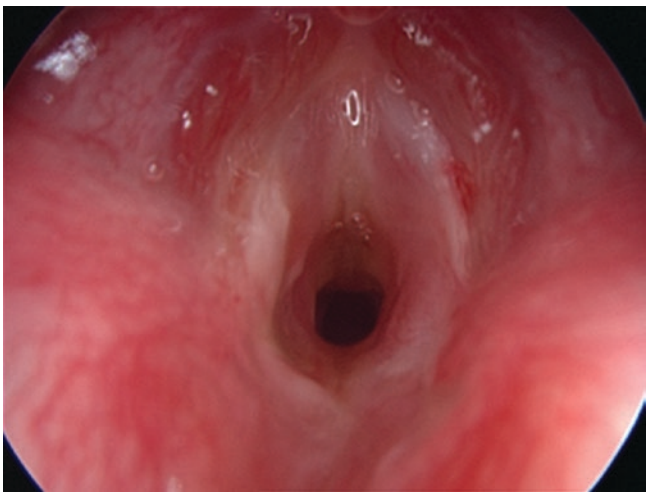

Fig. 10.13 Closer view of the larynx of the same patient is shown in Figure 11. The damage caused by the endotracheal tube can be seen extending into the subglottic and upper tracheal regions

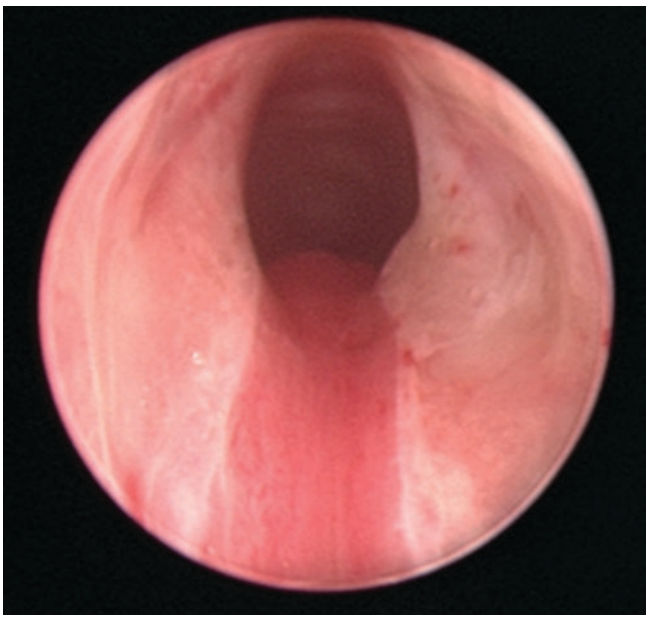

Fig. 10.14 Complete ulceration of mucosa from the endotracheal tube can lead to exposure of cartilage of the arytenoid and cricoid. This is typically seen in the posterolateral positions of the larynx. This can lead to chondritis, formation of granulation tissue with subsequent fibrosis and ultimately stenosis

opment of subglottic scarring and stenosis as described below {Jefferson, 2016 #21}.

Acquired Subglottic Stenosis: Acquired subglottic stenosis is narrowing of the subglottic larynx as a consequence of laryngeal injury. It can result from high tracheostomy, neck injury, laryngeal burn or infection, but over 90% relate to endotracheal intubation [28]. The incidence of subglottic stenosis associated with endotracheal intubation has fallen over the decades as medical knowledge and procedures have improved, particularly in relation to the appropriate size of endotracheal tubes for the size and age of the child [18]. The conventional incidence of subglottic stenosis after the 1990s has been approximately 1% of intubated neonates and children [32]. However, the range extends from 0% to as high as 11% [87, 88]. Unlike congenital subglottic stenosis, acquired stenosis does not improve over time, although children with milder stenosis and symptoms may be followed conservatively [32].

The developmental sequence of intubation-associated acquired subglottic stenosis is mucosal edema, mucosal ulceration and necrosis, varying degrees of cricoid and arytenoid cartilage necrosis, inflammation, granulation tissue formation, squamous metaplasia, reactive fibroplasia, and scar tissue retraction [82, 89]. The relation of duration of endotracheal intubation to the development of subglottic stenosis is not clearly defined, although Manica et al. in a prospective study reported a relatively small cohort of postintubation children followed by regular flexible fiber-optic laryngoscopy demonstrated an increased risk of development of subglottic stenosis over time [90]. As with congenital subglottic stenosis the Myer-Cotton classification of severity is widely applied [36]. The symptoms of acquired subglottic stenosis generally are the same as those of congenital subglottic stenosis, and include stridor, brassy cough, respiratory distress, cyanosis, and failure of decannulation in a child not previously suspected to have subglottic stenosis [28, 32].

Treatment of acquired subglottic stenosis depends on the child's symptoms and Myer–Cotton classification. Children with acquired subglottic stenosis of Myer–Cotton Grade I and II and minimal symptoms may be watchfully followed or receive balloon dilatation and not require surgery. Surgery is usually required for Grade III and IV severity. Options depend on the severity and extent of the stenosis and include anterior or posterior graft laryngotracheal reconstruction, cricotracheal resection with end-to-end anastomosis, and high slide tracheoplasty. Complications to the open procedures are suture dehiscence, graft displacement, infection, and granulation tissue formation [32, 91].

Other Upper Airways Injuries: Granulation tissue nodules or polyps (Fig. 10.15) and subglottic cysts (Fig. 10.16) have been reviewed in this chapter. Other injuries or conditions associated with endotracheal intubation include accidental intubation of the esophagus, bronchial intubation, esophageal or tracheal perforation, mucus or blood obstruction of the endotracheal tube and infections [73, 92–95]. These generally are not within the surgical pathologist's scope of practice.

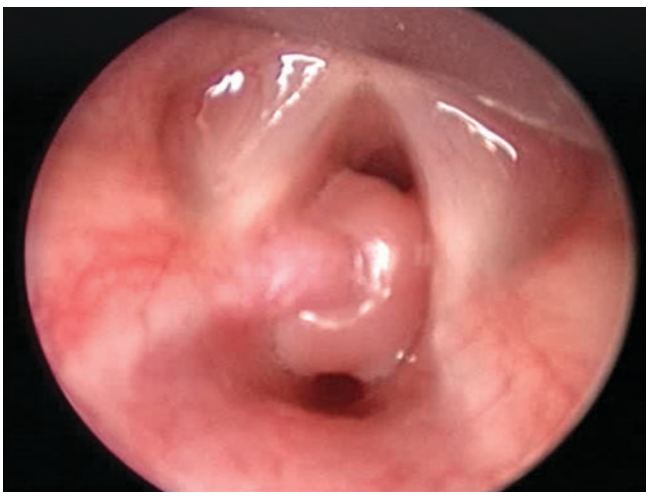

Fig. 10.15 Granulomatous polyp arising from the left vocal process can be seen as a late complication of endotracheal intubation. In children, these polyps can often present with airway obstruction as well as persistent hoarseness, a presenting symptom more commonly seen in the adult population

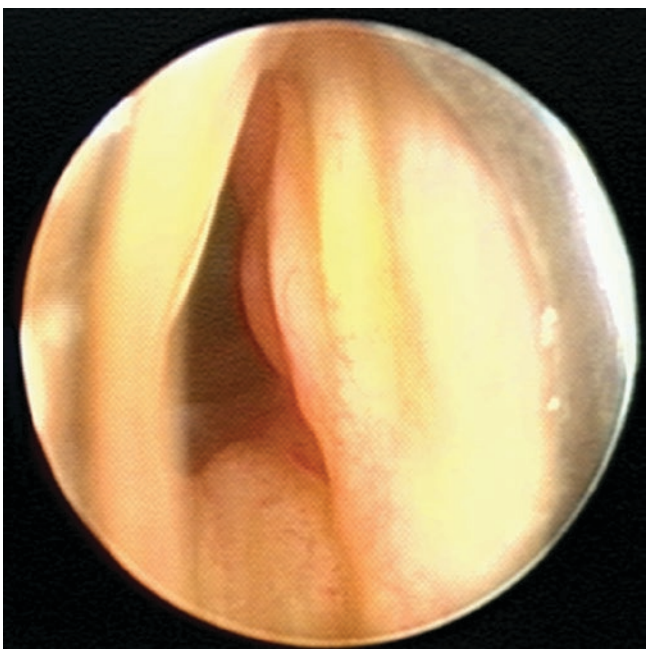

Fig. 10.16 Subglottic cysts can form secondary to obstruction of mucous secreting glands from prolonged intubation. Cysts can be seen directly below the right vocal cord and in the posterior subglottis

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