Rare Diseases of Larynx, Trachea and Thyroid

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ABSTRACT

This review article covers data on rare diseases of the larynx, the trachea and the thyroid. In particular, congenital malformations, rare manifestations of inflammatory laryngeal disorders, benign and malignant epithelial as well as non-epithelial tumors, laryngeal and tracheal manifestations of general diseases and, finally, thyroid disorders are discussed. The individual chapters contain an overview of the data situation in the literature, the clinical appearance of each disorder, important key points for diagnosis and therapy as well as a statement on the prognosis of the disease. Finally, the authors refer to study registries and self-help groups.

Contents

1 Introduction

The treatment of rare diseases represents a particular challenge. This article comprises a summary of rare diseases of the larynx and the trachea. Another short chapter is dedicated to rare diseases of the thyroid gland. The following overview does not claim to be complete, it will rather focus on several main aspects of the topic. Beside malformations, specific types of inflammations and laryngeal manifestations of general diseases, the manuscript illustrates in particular benign and malignant tumor diseases. This overview will focus on entities for which sufficient data material is available in the literature, mainly in form of case reports or rarely as reviews. Most of the cited articles were published in German or English. The respective diseases will be briefly summarized in order to achieve a significant overview while keeping the word limitations of the article. For more detailed information we will refer to the cited literature. Within the article, the term of "patient" is used for affected persons, which include all genders. Patient registries and databases allow an improvement of clinical research, optimized care and treatment for patients with rare diseases. One example is the Orphanet database. The website entitled www.orpha.net provides information on registries, current research projects, and trials on rare diseases as well as contact data of self-help organizations. In addition, European networks for care and treatment of patients with rare diseases are founded currently. In this context, the homepage of the European Reference Networks (ERN) of the European Commission shall be mentioned.

2 Malformations

Malformations of the larynx and trachea are congenital and belong to the group of rare diseases. Besides stenoses they also include clefts and fistulas. In the following chapter, the most important congenital malformations are illustrated.

2.1 Laryngomalacia

Laryngomalacia is the congenital laryngo-tracheal malformation with the highest incidence and most frequent reason for connatal stridor in newborns and infants [1]. Numerous publications are found on this disease. An immature, instable cartilaginous skeleton of the larynx is assumed to be responsible for laryngomalacia. This instability leads to a collapse of the supraglottis with consecutive stridor especially in context with forced inspiration. Mostly, the epiglottis is affected. Additionally, a relative hypertrophy of the arytenoid mucosa is observed. Differential diagnostics must exclude other origins of laryngo-tracheal stenoses. 45–75 % of all pediatric cases with stridor are associated with laryngomalacia [2, 3].

Clinical manifestation

Typically, the symptoms already occur shortly after birth. An inspiratory stridor is inevitable especially in the context of forced inspiration. Dysphagia with aspiration have been described. In severe cases, the oxygen saturation decreases with resulting cyanosis.

Diagnostics

In cases of laryngomalacia, transnasal flexible endoscopy under spontaneous breathing is the standard diagnostic procedure. Phonation and respiration but also swallowing can be reliably assessed this way. A well-instructed team and the involvement of the accompanying person (parent) is crucial in order to achieve high quality endoscopy despite defense reactions of the child. Attention must be paid to the risk of possible emergency situations due to acute laryngospasms. For classification (e. g. according to Olney [1999], see ▶ Table 1) and planning of further procedures, rigid endoscopy under sedation with and without spontaneous breathing is optimal. In 10–20 % of the cases, further pathologies such as subglottic stenoses or vocal fold pareses are associated with laryngomalacia [4–7].

Therapy

The decision pro/contra surgical treatment is made based on the clinical overall impression. Crucial criteria are stridor with resting dyspnea, respiration-related nutritional problems, failure to thrive, obstructive sleep disorders, stress-related hypoxia and hypercapnia and cyanosis [9, 10]. The surgical therapy is orientated on the classification of laryngomalacia according to Olney. As first measure, a so-called transoral microlaryngoscopical supraglottoplasty is performed. The mucosa in the arytenoid region is partially resected with preservation of the posterior commissure and an incision of the aryepiglottic folds (most frequently) or – in rare cases – epiglottopexy or individual combination of these three measures is performed. Epiglottopexy means a fixation of the epiglottis to the base of the tongue by suture, which prevents a collapse of the epiglottis into the laryngeal aperture [11].

▶ Table 1 Classification of laryngomalacia according to Olney (1999) [8].

Olney type 1	Mucosal prolapse of the arytenoid region/hypertrophy of the accessory laryngeal cartilage
Olney type 2	Short aryepiglottic folds
Olney type 3	Dorsal displacement of the entire epiglottis

Prognosis

In 90 % of the cases, the surgical intervention leads to a significant improvement of regular respiration [12, 13]. The complication rates are low, however, rarely dysphagia and aspirations may occur. The rarest and also severest complication is a supraglottic stenosis which can be avoided by reluctant resection of the mucosa [14]. If comorbid disorders are found, these may influence and deteriorate the postoperative outcome [12].

Note: Depending on the severity, laryngomalacia may be a life-threatening disease. Supraglottoplasty in the context of microlaryngoscopy leads to restitution of the respiratory function with a low complication rate.

2.2 Congenital bilateral vocal fold palsy

After laryngomalacia, congenital bilateral vocal fold palsy are the second most common cause of congenital stridor [15]. Murty et al report about an incidence of 0.75 per 1 000 000 births [16].

Clinical manifestation

The congenital bilateral vocal fold palsy is always an acute disease with dyspnea, cyanosis, and cervical retractions. In general, immediate intubation is required to secure respiration.

Diagnostics

By means of flexible endoscopy, the mobility of the vocal folds can be assessed. In newborns, the diagnosis requires an enormous experience due to the anatomical situation as well as secretory retentions which complicate endoscopy. General or comorbid disorders should be excluded by an interdisciplinary team. EMG of the larynx is controversially and very critically discussed because of the difficult performance and assessability [10].

Therapy

Intubation is necessary in most of the cases. While older publications mention tracheostomy as unique and permanent therapeutic option, more recent articles also recommend endolaryngeal surgery, e. g. partial unilateral laser chordotomy modified according to Kashima [17–22]. Spontaneous regeneration of the vocal fold mobility within the first 12 months of life have been described [23] so that interventions that might have irreversible consequences in the sense of scarring and dysphonia are recommended only after the 12th month of life [24].

Prognosis

According to the literature, up to 80 % of the cases require tracheostomy as initial airway management. In 29–71 % of the cases, the vocal fold mobility starts spontaneously after 6 months to 11 years. Partial chordotomy is recommended after the 12th month of life in cases of persisting symptoms. All these procedures lead to dysphonia and impaired respiratory function. The potential morbidity of children with tracheostoma must be taken into account.

Note: The therapy of congenital bilateral vocal fold palsy is an interdisciplinary challenge involving pediatricians as well as otolaryngologists/phoniatricians.

2.3 Laryngeal clefts

In the literature, 214 publications are found dealing with diagnostics, therapy, comorbidities, and complications of laryngeal clefts. The occurrence of occult, non-symptomatic small laryngeal clefts seems to be rather high. The number of publications has continuously increased during the last years due to improved diagnostic options.

Clinical manifestation

The incidence of laryngeal clefts amounts to 0.5–1 per 100 000 live births [25, 26]. Male newborns are more frequently affected than females. The development of laryngeal clefts is based on a disturbed fusion of the tracheoesophageal septum in the 5th to 7th week of embryogenesis [27]. While laryngeal clefts appear as isolated disorder in most cases, they may also be part of a general syndromatic l disease, e. g. Opitz G/BBB syndrome, CHARGE or VACTERL association [28, 29]. Laryngeal clefts are classified according to Benjamin and Inglis (▶ **Fig. 1** and ▶ **Table 2**).

The clinical symptoms of a type 1 cleft are mostly unspecific: difficulties in drinking, intra- and postdeglutitive cough, bronchopulmonary infections up to pneumonias requiring inpatient treat-
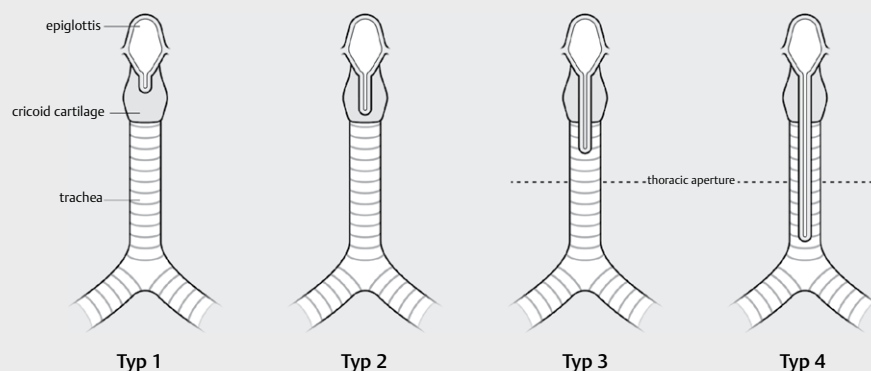
▶**Fig. 1** Laryngeal clefts. **Type 1** The laryngeal cleft only concerns the postcricoid region and ends without cartilage involvement above the level of the vocal folds. **Type 2** The laryngeal cleft draws into the cricoid cartilage and ends below the level of the vocal folds. **Type 3** There is also a cleft of the trachea, which ends above the thoracic aperture. **Type 4** The tracheal part of the cleft draws beyond the thoracic aperture just above the bifurcation.

ment [28–31]. The primary diagnosis is often delayed. Whereas the symptoms of type 3 or type 4 cleft become apparent mostly within the first minutes or hours after birth, type 1 and type 2 are frequently discovered only in the further course [32].

Diagnostics

The gold standard in the diagnostics of laryngeal clefts is rigid endoscopy under general anesthesia with palpation of the posterior larynx [32]. In most cases, X-ray or CT scan of the thorax are performed prior to endoscopy. Flexible endoscopy in the awake patient or functional swallowing examination may give hints on a cleft but they cannot exclude it in case of regular findings [33].

Therapy

In cases of type I clefts, wait-and-see strategy over 6 months is often sufficient with adaptation of the nutrition (up to feeding tubes non per os) as well as therapy of bronchopulmonary infections [29, 34, 35]. In most cases, the normal growth leads to regression of the symptoms so that surgical intervention is only rarely required in type I clefts [30, 33, 36, 37]. However, if the symptoms are still present after 6 months, the indication of surgical treatment is given. While type I and sometimes II can be sufficiently treated by microlaryngoscopy including suture techniques or augmentation, type III clefts require an open approach, type IV even thoracotomy [38, 39].

Prognosis

In type I and II laryngeal clefts, a posttherapeutic healing rate of up to 94 % is described. The revision rate amounts to less than 5 % [35]. Larger clefts of type III or IV require a challenging management beside tracheostomy and an open, median (thyrofissure) or lateral surgical approach. One critical complication is the postoperative tracheoesophageal fistula. Depending on possible congenital general diseases, the mortality in type III and IV clefts amounts to about 50 % [38, 40, 41].

Note: The therapy of laryngeal clefts depends on their severity. Smaller clefts with mild symptoms should be observed and treated symptomatically during the first 6 months. In the further course, endoscopic treatment may be necessary. Sever clefts of type III and IV usually become symptomatic immediately after birth and require an extensive management including tracheostomy.

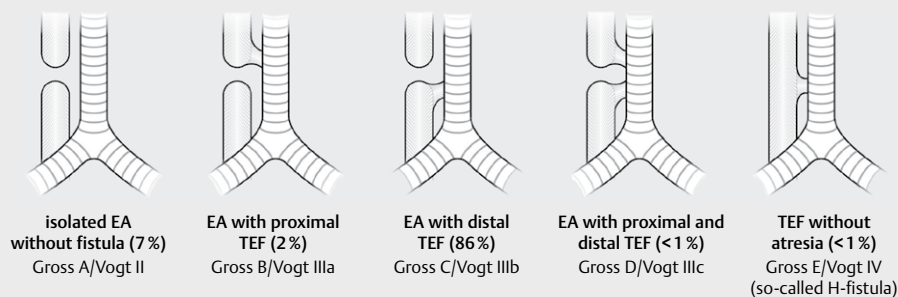## 2.4 Tracheoesophageal fistulas and esophageal atresia

In the literature, more than 5000 publications are found on this topic. They cover case reports, original papers on diagnostics and surgical procedures as well as numerous review articles.

Clinical manifestation

The development of tracheoesophageal fistulas (TEF) is not yet finally clarified since its first description by Gibson in 1697 [42]. Missing formation of the esophageal septum as well as disturbed development of the embryonic bronchial structures are discussed [42, 43]. In 90 % of the cases, congenital TEF are associated with esophageal atresia, their incidence is estimated to about 1 of 3500–4500 live births [44, 45]. The clinical appearance of TEF depends on the severity of the esophageal atresia and the type of fistula. The classification of esophageal atresia is based on the description of the American radiologist Edward Vogt (▶ **Fig. 2**) [46]. A tracheoesophageal fistula is observed in cases of type IIIa, IIIb, IIIc, and IV, the so-called H fistula [47]. In cases of esophageal atresia, the drainage of the amniotic fluid is impeded so that a polyhydramnios is pathognomonic [48]. Type IIIb is seen most frequently. Beside nutritional impairment, affected newborns also show dyspnea and stridor. Furthermore, aspiration pneumonia may appear due to regurgitation of the stomach content via the fistula into the trachea.

▶ **Table 2** Laryngeal clefts according to Benjamin and Inglis (1989).

Type 1	**Supraglottic interarytenoid defect, the cleft is located above the cricoid cartilage**
Type 2	Partial cleft in the cricoid cartilage with subglottic extension
Type 3	Total cleft of the cricoid cartilage and tracheal (above the thoracic aperture)
Type 4	Type 3 with extension of the cleft beyond the posterior tracheal wall and maximum extension to the carina

| isolated EA without fistula (7 %) Gross A/Vogt II | EA with proximal TEF (2 %) Gross B/Vogt IIIa | EA with distal TEF (86 %) Gross C/Vogt IIIb | EA with proximal and distal TEF (<1 %) Gross D/Vogt IIIc | TEF without atresia (<1 %) Gross E/Vogt IV (so-called H-fistula) |

▶ **Fig. 2** Tracheoesophageal fistulas. **Gross A/Vogt II** An atresia of the esophagus is found without development of tracheoesophageal fistula. In this case, no air is accumulated in the stomach. **Gross B/Vogt IIIa** Esophageal atresia is found with tracheoesophageal fistula at the upper segment. The lower segment ends blindly. **Gross C/Vogt IIIb** Esophageal atresia is found with tracheoesophageal fistula. The upper segment ends blindly. This is the most frequently observed type of esophageal atresia. **Gross D/Vogt IIIc** Esophageal atresia is found with fistula development and upper segment. **Gross E/Vogt IV** Tracheoesophageal fistula is found without presence of esophageal atresia (so-called H fistula).

In the context of a so-called H fistula between the esophagus and trachea with regular patency of the esophagus, early pulmonary symptoms such as aspiration, cough, or even suffocation may result. Smaller H fistulas can also be asymptomatic [49]. In more than 40 % of the cases, esophageal atresia with/without TEF is associated with other – mainly cardiac – malformations and appears also in the context of syndromes.

Diagnostics

Before birth, the first suspicion arises due to the presence of polyhydramnios. Therefore, in rare cases the diagnosis can already be made before birth. The clinical suspicion implicates the recommendation of delivery in a center with according experience and equipment. The impossibility to completely explore the esophagus with a nasogastric tube (not more than 10–15 cm) indicates the presence of esophageal atresia. By means of X-ray, the tube can be displayed in the upper esophageal sac. In addition, air-fluid levels are typically seen. The use of barium contrast agent is obsolete since it may induce pneumonitis. Fistulas and atresias may be well examined by endoscopy, which is essential for planning an intervention. Esophageal atresia is often associated with syndromic diseases (e. g. trisomy 18) [50, 51].

Therapy

The responsibility of the therapy is with the pulmonary/pediatric surgeons. Surgeries of the thoracic area in the sense of end-to-end anastomoses can be performed via an open approach (which is associated with high morbidity) or as minimally invasive procedure. The fistulas are closed surgically [52, 53]. Smaller TEF can be closed with fibrin glue. Insufficiencies of the anastomoses occur frequently in 20 % of the cases and are treated conservatively.

Prognosis

The risk of post-therapeutic esophageal stenosis amounts to 25–40 %; therapy consists of repeated dilatations. The post-therapeutic mortality of 5–10 % is influenced among others by comorbidities [50]. Affected patients may contact the self-help organization for esophageal diseases called KEKS.

Note: Esophageal atresia is mostly associated with tracheoesophageal fistula. Therapy consists of surgery; the post-therapeutic morbidity is relatively high.

2.5 Laryngeal web (diaphragm)

In the literature, about 200 publications are found on the management of this disease.

Clinical manifestation

The congenital glottic web or diaphragm was first described in 1882 by Fleischmann. These webs make up about 5 % of the congenital anomalies of the larynx and are caused by missing laryngeal recanalization during organ genesis [54, 55]. Sometimes they are associated with syndromes such as 22q11.2 deletion syndrome [56]. The congenital glottic web is classified according to Cohen. Depending on the severity of the glottic stenosis four types are differentiated. Type I causes glottic stenosis of less than 35 %, type II between 35 and 50 %, type III comprises 50–75 % of the glottic surface and always reaches to the anterior cricoid part in the subglottis. In

type IV, a stenosis of 75–99 % is found. The complete congenital laryngeal stenosis is called "congenital high airway obstruction syndrome" or CHAOS (see tracheal agenesis) [57, 58]. In grade I and II, the vocal folds are still defined, smaller findings may sometimes remain clinically undetected. In grade III and IV, the differentiation of the vocal folds is nearly impossible.

Due to the different degrees of stenosis, the clinical symptoms of the affected patients may vary. Patients with type I findings are often asymptomatic. Others report about dysphonia that also persists when patients cry. The symptoms may worsen in cases of infection of the upper airways. Grade III and IV may impose by highly relevant persisting dyspnea with stridor as of birth [59].

Diagnostics

Newborns with dysphonia and stridor should be examined by an ENT specialist with pediatric expertise. The diagnosis is made by transnasal flexible endoscopy. Rigid endoscopy under sedation with and without spontaneous breathing is essential in order to assess the severity of the anomaly. In these cases, special attention is necessary so that no further scarring by inadequate intubation is caused.

Therapy and prognosis

Small asymptomatic congenital glottic webs may first undergo wait-and-see strategy. If surgery becomes necessary due to worsening of the symptoms, it should be performed endoscopically in cases of small findings. Different procedures are applied such as balloon dilatation and transection of the web with the CO_2 laser. It must be observed that most webs reach into the subglottic area which can make the temporary insertion of a silicone keel necessary. Grade III and IV webs sometimes require initial tracheostomy with subsequent reconstruction that is usually performed in several steps [60]. In summary, tracheostomy should be avoided if possible. In cases of congenital glottic webs of grade III and IV, open approaches are preferred [61].

Note: In most cases, glottis webs reach into the cricoid cartilage and therefore the simple transection does not generally suffice as therapy.

2.6 Tracheal agenesis

In the literature, about 200 publications on the topic of tracheal agenesis are found. The reason for the development of tracheal agenesis is not clarified. Theories exist about the displacement of the esophagotracheal septum in dorsal or ventral direction during embryogenesis [62].

Clinical manifestation

Tracheal agenesis (TA) was first described in 1900. Since then, only few cases have been published. The prevalence amounts to about 1 of 50 000–100 000 live births with a ratio of 2:1 regarding male and female patients. In general, the disease has a lethal outcome. In most cases, it is diagnosed before birth when a so-called CHAOS syndrome (see above) is detected. However, a CHAOS syndrome cannot develop in cases of tracheoesophageal fistula so that the diagnosis in these cases can only be made shortly after birth.

According to Floyd, three types are classified (▶ **Fig. 3**). Type I (20 %) consists of an agenesis of the upper trachea, a fistula is found between the trachea and the esophagus, the bronchi are regular.

Type II (60 %) consists of complete tracheal agenesis, the bronchi are regular and a fistula is found between the carina and the esophagus. In cases of type III, the main bronchi separately exit from the esophagus [63, 64] (▶ Fig. 4). TA is rarely observed as isolated malformation, in up to 94 % other congenital anomalies are present, e. g. VATER association (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial or renal dysplasia). The leading symptom is severe stridor after birth that unfortunately has a rapid lethal outcome [65].

Diagnostics

In general, polyhydramnios can be identified during pregnancy by means of ultrasound. Furthermore, also the trachea can be well displayed in prenatal diagnostics [66]. Severe dyspnea and the associated impossibility of endotracheal intubation are cardinal symptoms of TA.

Therapy and prognosis

Patients with complete TA cannot survive. The results of surgical therapy of TA are disillusioning up to now. Only four cases are found in the literature with short survival periods. Multidisciplinary approaches are required in this context. No reports are available about patients who have reached toddler age [62].

Note: Tracheal agenesis is not compatible with life even if the diagnosis is already made before birth.
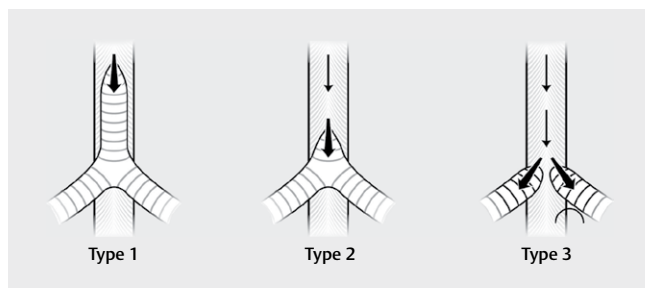
▶ Fig. 3 Tracheal agenesis. **Type 1** A tracheal stump is found above the bifurcation into which a fistula opens from the cervical esophagus; incidence of 20 %. **Type 2** A tracheal stump does not exist, the bifurcation is directly connected with the esophagus; incidence of 60 %. **Type 3** In this case, also the bifurcation is missing, both main bronchi open separately into the esophagus; incidence of 20 %.

3 Rare types of laryngitis

The unspecific acute and chronic laryngitis is a frequent disease that may have manifold origins. Among acute as well as chronic types, rare subgroups are found. Rare types of acute laryngitis comprise ulcero-membranous laryngitis, which is a group of different diseases that are characterized by fibrinous deposits on the mucosa. Classic examples are diphtheria and the ulcero-membranous Plaut-Vincenti disease [67]. In the last 10 years, no articles have been published due to the rarity of the cases of laryngeal diphtheria so that it is only mentioned here. The rare types of chronic laryngitis include some specific inflammatory diseases, in first place laryngeal tuberculosis that will be dealt with in the following chapter. Furthermore, leprosy of the larynx will be discussed. Laryngeal syphilis is extremely rare. Primary, secondary, and tertiary affections typically manifest rather in the oral cavity and the oropharynx and only in very rare cases in the larynx. In the current literature, only one case is reported [68].

3.1 Laryngeal tuberculosis

In the literature, more than 700 publications are found on laryngeal tuberculosis. They appeared mainly in the 1950ies, but also in the last years, articles were regularly published on this topic.

Clinical manifestation

Globally, tuberculosis represents a relevant disease. However, in Europe – especially in Germany – it ranks among the rare diseases. Males are twice as much affected than females. In general, young adults acquire this disease. The association with an HIV infection is found in up to 50 % [69]. Endoscopy shows ulcera as well as hypertrophic granulation manifestations [70]. All areas of the larynx can be involved, however, the vocal folds are more frequently affected than other regions. In the older literature, posterior laryngeal parts were defined as predilection sites; the reason for this is supposed to be the retention of infectious sputum from the deep airways in the postcricoid region. More recent systematic observational trials, however, could not confirm this assumption. Typically, only one side is affected, e. g. as so-called monochorditis of one vocal fold [71]. Due to the unspecific appearance, laryngeal tuberculosis may be endoscopically mis-diagnosed as laryngeal cancer. In nearly all patients, the chest X-ray is conspicuous even if only part of these patients suffer from chronic cough.
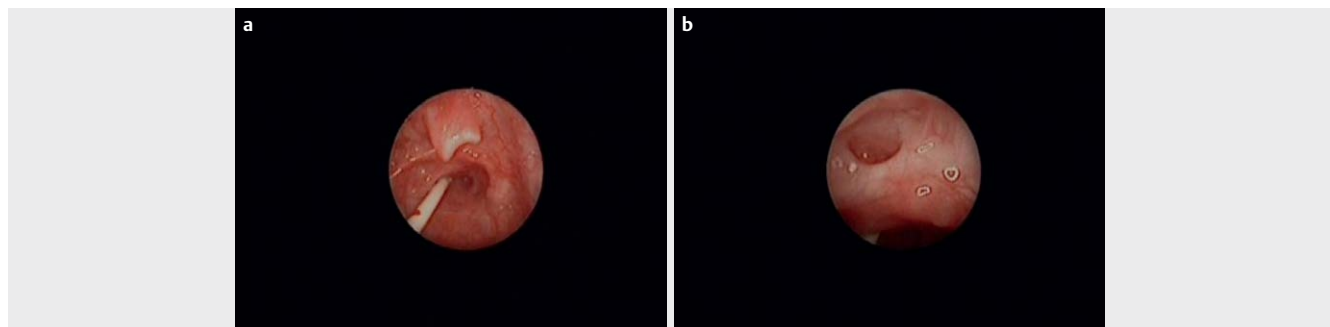
▶ Fig. 4 **a** Tracheal agenesis in a newborn. The epiglottis is developed, the laryngeal lumen is closed. Ventilation of the patient via the esophagus and the esophago-bronchial fistula is performed. **b** Tracheal agenesis in a newborn. Now with uploaded epiglottis and visibly free esophageal lumen and completely closed laryngeal lumen.

Diagnostics

The diagnosis is confirmed by biopsy with histological detection of caseous epitheloid-cell granulomas and acid-fast bacilli in the Ziehl-Neelsen staining or PCR as well as sputum analyses with the cultural proof of Mycobacterium tuberculosis [72]. Nearly all patients have additional pulmonary affection so that chest X-ray is highly relevant [73]. In general, the sputum culture is positive, however, this examination takes much time due to the long duration of cultivation. The disease occurrence and tuberculosis-related deaths as well as the microbiological detection of Mycobacteria have to be reported to the health authorities.

Therapy

After the diagnosis has been confirmed, therapy should be initiated as soon as possible. Regression of the laryngeal lesions usually starts some weeks after therapy onset. In general, tuberculostatic therapy is performed over 6 months [74]. However, scars develop very regularly, especially in the larynx. Typically, fixations of the cricoarytenoid joint, posterior glottic stenoses, or subglottic stenoses occur with resulting persistent dysphonia and stress-related dyspnea.

Prognosis

With adequate therapy, the prognosis of the patients with regard to complete healing of the disease is very good. However, complex scarring is observed frequently, which is very difficult to treat and leads to functional impairment [75].

Note: Monochorditis is a typical manifestation of laryngeal tuberculosis.

3.2 Leprosy of the larynx

Only sporadic case reports on leprosy of the larynx are found in the literature or the publications are several decades old.

Clinical manifestation

The disease is caused by Mycobacterium leprae and is nowadays mainly found in tropical and subtropical areas of Asia, especially in India. Long-lasting and close physical contact is a precondition for infection, so that the disease often affects people who live together in narrow conditions. Since lower temperatures promote cell division of leprosy bacteria, the nasal mucosa is particularly colonized and is thus considered as pathogen reservoir and main infection source. The development of granulation tissue (lepromas) is typical. It surrounds preferably the peripheral nerves and destroys them in the further course. In cases of leprosy manifestations of the nasal mucosa, laryngeal affection is observed in about 30 % of the cases. Lepromas are nearly exclusively found on the prominent parts of the larynx, i. e. the free edge of the epiglottis where they appear as tumor-like distended masses.

Diagnostics

According to the recommendations of the Robert-Koch Institute (www.rki.de), the diagnostics is based on histological examination or the identification of specific DNA by PCR from skin or mucosal biopsies. Sometimes, detection of pathogens is also possible in the lymphatic fluid, which is harvested by scratching the skin at predefined sites. Disease occurrence and/or death have to be reported to the health authorities.

Therapy and prognosis

The treatment of leprosy is oriented at the therapy of tuberculosis. Poly-drug-therapy is performed for several months. In the larynx, the lesions heal with scar formation. In addition, sensitivity disorders are described because of damage of the superior laryngeal nerve with resulting aspiration pneumonia [67, 76]

Note: Lepromas preferably manifest in close neighborhood to peripheral nerves and lead to sensitivity disorders. Manifestation in the larynx may lead to aspiration.

3.3 Laryngeal leishmaniasis

Leishmaniasis is an infectious granulomatous disease that may be caused by the protozoae *Leishmania (L) brasiliensis, L. amazonensis, L. panamensis,* or *L. guyanensis*. The primary vectors are sand flies [77]. The disease is classified into three clinical manifestations: the visceral type (Kala-Azar), the cutaneous type, and the mucocutaneous type. Mucosal leishmaniasis generally manifests after hematogenic distribution over months and years after skin infection [78]. It is often observed in Latin America, the pathogen is *L. brasiliensis* [79]. The occurrence of mucocutaneous manifestations depends on the virulence of the parasites and the immunocompetence of the host. Hence, even in endemic regions it is a rare disease. Most frequently, the nose, pharynx, larynx, and oral cavity are affected. Infection usually occurs in the context of journeys to foreign countries. The Robert-Koch Institute reports about 20 cases each year in Germany.

Clinical manifestation

In general, laryngoscopy shows extended inflammatory lesions with erythema and edema. Purulent exudation may be observed. In advanced cases, tissue destruction occurs which can be extended and is often misinterpreted as malignant disease.

Diagnostics

The diagnosis of leishmaniasis is based on direct cytological or histological evidence of intracellular parasites. Furthermore, immunological tests are available, e. g. the identification of antibodies in the immunofluorescence or via ELISA. PCR has the highest sensitivity and specificity that is performed with bone marrow or skin specimens or also with peripheral blood. Most decisive is biopsy and travel history taking.

Therapy and prognosis

An adequate therapy of the cutaneous lesions can reduce the risk of mucosal disease which may appear even years after primary infection [80]. The therapy of choice is the application of liposomal amphotericin B (AmBisome, e. g. Gilead Science GmbH, Martinsried, Germany). Miltefosin p.o. (Impavido, Paesel und Lorei GmbH & Co. KG, Rheinberg, Germany) is considered as measure of second choice. Theoretically, the disease is curable by adequate therapy, however, complete healing is not possible in many cases. Especially the cutaneous type often leads to disfiguring scar formations. In the context of diagnostics, also the immunocompetence of the patient should be verified (HIV test). The primary prophylaxis (application of repellents) is of particular importance.

Note: Laryngeal leishmaniasis may develop even years after skin manifestation. Due to its clinical appearance, it may be misdiagnosed as laryngeal carcinoma.

4 Benign tumors

4.1 Benign epithelial tumors
4.1.1 Juvenile and adult papillomas

A large number of publications on recurrent respiratory papillomatosis can be found in the literature with more than 800 original articles and reviews. In the current overview, the disease will be briefly summarized. The authors want to refer to the numerous comprehensive review articles on this topic.

Clinical manifestation

Laryngeal papillomas are the most frequently observed benign epithelial tumors of the larynx [81]. The difference is made between two types: The juvenile type, which is diagnosed before the age of 12 and generally occurs in young children and the adult type, that mainly affects young, preferentially male adults [82]. Both types have a comparable incidence of 2–4 per 100 000 people and thus count to orphan diseases. Laryngeal papillomatosis is caused by different subtypes of the human papilloma virus (HPV), mainly HPV Type 6 and 11. HPV Type 11 seems to be associated with more aggressive courses. The manifestation within transition zones between various epithelia (e. g. between squamous epithelium and respiratory epithelium) is typical. Laryngeal papillomas are found especially at the vocal folds [83]. The infection pathway is still not fully understood. Peripartal infection is assumed to be the reason for the juvenile type. A correlation can be identified with the presence of maternal anogenital papillomas. Regarding the adult type, sexual infection pathways are additionally discussed [84]. The clinical appearance depends on the location and the size of the papillomas. Chronic hoarseness and – at later stages - obstruction of the airways are typical symptoms. In most cases, the papillomas concern the laryngeal mucosa. Tracheal or even bronchial extension is very rare and associated with a particularly poor prognosis [85].

Diagnostics

Indirect laryngoscopy may already allow a diagnoses in many cases. Papillomas are characterized by a cauliflower-like surface with a specific vascular pattern (▶ **Fig. 5**). Histological examination provides the evidence. The detection of HPV DNA in the tissue is nowadays diagnostic standard. Special imaging procedures, e. g. narrow-band imaging or comparable techniques, may be helpful to identify also small manifestations [86].

Therapy

Usually, the removal of disturbing or critically extended papilloma foci is performed by transoral microsurgical procedures. Such resections are strictly limited to the epithelium because the virus does not affect the subepithelial tissue. Radical resections are obsolete, they do not avoid recurrences, but they harm the functionality of the larynx. Recurrences generally develop in adjacent mucosal areas that are also infected by the virus. Repeated session are frequently necessary to remove the papillomas by different measures, based on the individual symptoms. The occurrence of recurrences is pathognomonic for the disease. Surgical and pharmacotherapies will only briefly be mentioned in this chapter, the authors refer to the specific literature. In Europe, therapy of choice is often CO_2 laser surgery with tissue preserving evaporation of the papil-
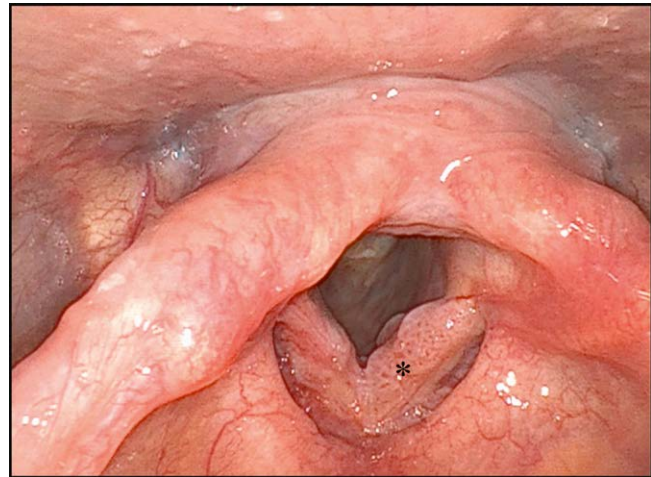
▶ **Fig. 5** Papillomatosis. (*) Laryngeal papillomatosis (here: HPV type 6) with pathognomonic vascular loops; flexible laryngoscopy (chip/tip).

lomas. In the US, shaver procedures are primarily applied. The more recent literature describes the application of new types of lasers. There are numerous publications on drug-related therapy. Pharmacotherapy aims at prolonging the intervals between surgeries and has to be considered as adjuvant measure. Interferon-alpha represented the first treatment strategy to support the immune system in papilloma patients. However, the medication is only rarely applied today due to relevant systemic side effects. Instead, the intralesional, partly also systemic application of bevacizumab (Avastin, e. g. Haemato Pharm GmbH, Schönefeld, Germany) and cidofovir (Tillomed Pharma GmbH, Ahrensberg, Germany) are in the focus today. The VEGF antibody bevacizumab is already routinely applied for example in ophthalmology. As angiogenesis inhibitor it can impede the new development of papillomatous foci. The use of cidofovir is discussed extensively in the literature, while a final assessment of the very different trials is problematic. In any case, repeated applications are necessary which may lead to relevant toxicity. More recent data on the COX-2 inhibitor celecoxib do not show any advantage for the patients. In a phase-II study, currently the effectiveness of pembrolizumab on the papilloma growth is evaluated [87]. Furthermore, there are small case series where the tetravalent vaccine Gardasil (MSD Vaccins, Lyon, France) has been applied in papilloma patients. Partly, promising results are found in small case series or in case reports. The pathophysiological mechanism of the preventive approach is not known up to now. However, it is assumed that in particular an infection of non-affected areas may be inhibited [88].

Prognosis

The recurrent respiratory papillomatosis is a disease that cannot be cured by current therapeutical measures. The prophylactic effects of comprehensive vaccination will be evident in the next decades. Prognostically, a rapid growth as well as an affection of the trachea are very unfavorable. Reports on malignant degeneration in adults are available, a malignant transformation rate of about 2 % is assumed [87].

Note: The objective of the therapy of laryngeal papillomatosis is the thorough removal of the papillomas with shaver or laser with preservation of the laryngeal function.

4.1.2 Pleomorphic adenomas

Pleomorphic adenomas of the larynx are very rare, in the literature 28 cases have been described.

Clinical manifestation

Adenomas in the area of the larynx originate from the seromucous glands and are histologically identical with the tumors of the salivary glands. The pleomorphic adenoma is the most frequently observed benign tumor of the major salivary glands. More rarely, the minor salivary glands are affected, and particularly rarely those in the larynx [89]. Monomorphic adenomas with tubular, acinar, or papillary histomorphology occur extremely rarely in the larynx. More frequently, but also very rare, pleomorphic adenomas are described [90]. The submucous masses are slowly growing and painless, clinical findings are unspecific. Radiologically and clinically, they cannot be differentiated from other benign tumors. Rarely, malignant transformation is observed, two cases have been described in the literature [90, 91]. Typical locations for pleomorphic adenomas are the supraglottis [92], the subglottis [93] and the trachea [94] with nearly equal incidences. Rarely, they manifest on the level of the glottis [95, 96]. The symptoms depend on the location and the size. Hoarseness, dysphagia, or (sometimes life-threatening) dyspnea are observed [93].

Diagnostics

Radiological imaging (CT scan and MRI) mainly aims at identifying the extension. Differential diagnostic classification is not possible. For this purpose, an excision (in larger tumors biopsy) with histological and immunohistological assessment is necessary. The pathologist must identify epithelial and myoepithelial-stromal components in order to verify the diagnosis. The expression of cytokeratin, S100, glial fibrillary acidic protein (GFAP), and vimentin are typical for pleomorphic adenomas [97].

Therapy

Surgery is the therapy of choice. The treatment concept should aim at preserving functional aspects beside complete tumor resection. Open accesses, e. g. via lateral pharyngotomy [95], and partly also transoral microsurgical resections are described [93, 98]. Recurrences have been reported as they are also found in other locations.

Prognosis

It remains open if the recurrences described in the literature are residual findings after incomplete removal or true recurrences. In the literature, also two cases of a carcinoma ex pleomorphic adenoma of the larynx are described, otherwise the prognosis seems to be favorable.

Note: The key for diagnosis is the immunohistological characterization, therapy optimally aims at complete tumor removal with at the same time preservation of the laryngeal function.

4.2 Benign non-epithelial tumors

4.2.1 Chondromas

In the literature, 85 publications are found. They include about 250 cases, among them three children [99].

Clinical manifestation

Beside chondrosarcomas, chondromas belong to the tumors of the laryngeal framework [100]. The incidence of chondromas and chondrosarcmoas within the group of all laryngeal neoplasms amounts to clearly less than 1 %. In 70–75 % of the cases, chondromas originate from the luminal side of the cricoid plate [101], followed by thyroid cartilage [102]. Single case reports also describe endolaryngeal chondromas at the arytenoid cartilage, mostly unilateral, in rare cases also bilateral [103]. Furthermore, Yang and Lin published the case of laryngeal chondroma of the epiglottis [104] and Ozcan et al. about chondroma of the hyoid [105]. Mostly adults younger than 50 years are affected while males are more frequently affected than females with a ratio of 4:1 [106]. Clinically, the tumors impose as hard, often spherical masses growing in- and outwardly and covered by regular mucosa. The symptoms vary according to the size and location of the tumors. Especially in endolaryngeal findings, dysphonia or increasing dyspnea with inspiratory stridor dominate. At the typical locations of the cricoid, the tumors grow also in direction of the esophagus entrance and may cause swallowing disorders. In some cases, chrondromas present as a palpable masses at the outer neck or as incidental findings in the context of imaging due to other reasons. Because of the slow growth, history often comprises several years. Cartilaginous tumors also appear in the trachea. These osteochondromas are sometimes detected as incidental findings during endoscopy. They are mostly small and do not require treatment.

Diagnostics

Comparable to all rare tumors, initial diagnoses are frequently incorrect. The most important imaging procedures are computed tomography and MRI. However, neither CT scan nor MRI can reliably differentiate between chondroma and chondrosarcoma. High-resolution computed tomography is recommended. It displays a tissue mass at the laryngeal framework originating from the cartilage. The most frequent radiological differential diagnoses are carcinomas with cartilaginous infiltration, laryngeal manifestations of chondromatosis or posttraumatic calcifications [107]. In the context of diagnostic microlaryngoscopy, tumors of the laryngeal framework may be diagnosed with high reliability [108]. Also here, a differentiation between chondroma and chondrosarcoma is not possible. Finally, histological examination is essential. It reveals hyaline cartilage formations similar to normal cartilage. The characteristics of chondromas in comparison to chondrosarcomas are a low percentage of cells, regular nuclei size and morphology as well as missing mitotic Fig.s. Chondromas and chondrosarcomas may also develop synchronously or metachronously [109].

Therapy

Chondromas are surgically resected, laryngeal preservation is an ultimate goal. In this context, generous open surgical therapies are mentioned, partly with temporary tracheostomy and multi-step reconstructions with rib cartilage [108]. Small glottic findings can also be removed by transoral microsurgery [103]. There is no evi-

dence in the literature regarding the difference between initial conservative function-preserving partial resections of chondromas with follow-up over many years or a primary radical surgery [101, 110]. In addition, reports about laryngectomy in cases of extremely large tumors are found [111].

Prognosis

An early diagnosis is desirable in order to perform possible function-preserving therapy. The tumors grow very slowly and patients need to undergo follow-up for a long time. Chondrosarcomas always have to be taken into consideration as differential diagnosis [102].

Note: The relationship of the tumor to the laryngeal framework is a typical characteristic as well as the slow growth and the hard consistency. A differentiation of chondrosarcoma is only possible by means of histopathology.

4.2.2 Lipomas

In the literature, currently 49 articles are found about laryngeal lipomas with a total of about 130 described cases.

Clinical manifestation

Generally, lipomas belong to the most frequent benign tumors in humans. They make up 4–5 % of all benign tumors. However, they are only rarely found in the larynx. About 0.6 % of benign laryngeal tumors are lipomas [112, 113]. Even more rarely, they are found in the trachea. They develop mostly after the 40th year of life, males and females are equally affected. Lipomas may occur at all locations of the larynx, including the vocal folds [114], the pre-epiglottic space [115] or combined extra- and intralaryngeal [112]. Mostly they present as isolated findings, but they may also occur in the context of generalized lipomatosis [116]. The symptoms are unspecific and depend on the location and size of the findings. Clinically, the tumors impose as soft, yellowish, partly lobular, partly polypous masses. In many cases, they reach into the laryngeal lumen or protrude the mucosa. Also life-threatening obstructions may develop. There are rare subtypes of lipomas of the larynx, e. g. spindle cell lipomas and pleomorphic lipomas. In this regard, eight cases have been described in the literature [117–122].

Diagnostics

In general, lipomas can be well displayed by ultrasound, however, the visibility is limited within the larynx due to the cartilage framework. MRI may clearly identify lipomatous tumors, however, a differentiation between lipomas and liposarcomas or lipoblastomas is nearly impossible [114]. Histologically, mature fatty tissue is found with delicate vessels and narrow connective tissue septa. CD34 positive, spindle-shaped cells with abundant fibrous and myxoid stroma, penetrated by abundant fatty tissue are typical for spindle cell lipomas [117].

Therapy

Surgical therapy is the only option for removal of the tumor. Open approaches are indicated in large or poorly accessible findings, otherwise the transoral microsurgery is preferred [118] or a combination of both [123]. More recent publications describe a removal via transoral robotic surgery [119]. Small incidental findings that have been discovered in the context of imaging can primarily

be controlled radiologically after histological assessment (differentiation of liposarcoma) if no functional impairment is observed.

Prognosis

In cases of incomplete removal, the residues may lead to further growth and new complaints. After complete resection, recurrences appear rarely. Follow-up over several years is recommended.

Note: The differentiation between lipoma and liposarcoma is only possible by means of histology and cannot be made by imaging. Complete extirpation should be aimed at.

4.2.3 Rhabdomyomas

In the literature, 34 reports about a total of 40 cases are found.

Clinical manifestation

Usually, rhabdomyomas are tumors of the cardiac muscles. Apart from the cardiac locations, the head and neck region is most frequently affected, especially the neck and face muscles as well as the muscles of the oropharynx and the tongue [124]. Laryngeal manifestations have been described, although they are extremely rare [125]. Male patients develop more frequently rhabdomyomas than females. The tumors usually appear as isolated findings and only rarely in the context of syndromes [126, 127]. Two different types are differentiated: the adult type, which appears more frequently in the larynx [128] as well as the fetal ones [127]. Hereby, the difference is made between cellular and myxoid subtypes. The symptoms are unspecific and depend on the size and location of the tumors. Usually, laryngeal rhabdomyomas originate from the M. vocalis but they may also affect the outer laryngeal muscles. This entity has not been described in the trachea up to now.

Diagnostics

In CT scans and MRI, rhabdomyomas impose as contrast enhancing sharply defined tumors. There is no clear differential diagnostic criterion. It is necessary to perform biopsy that shows polygonal vacuolized cells with fine-granular eosinophilic cytoplasm (▶ **Fig. 6**). The evidence is given by immunohistology with expression of desmin, myoglobin, muscle-specific actin (MSA), and negativity of cytokeratin, S100, CD68R, chromogranin A, and synaptophysin [129].

Therapy

The therapy of choice consists of complete surgical resection. Endoscopic as well as open approaches have been described. In most cases, phonosurgical reconstructions are necessary.

Prognosis

The prognosis is very good, only one report is available about a recurrence after complete surgical resection [130].
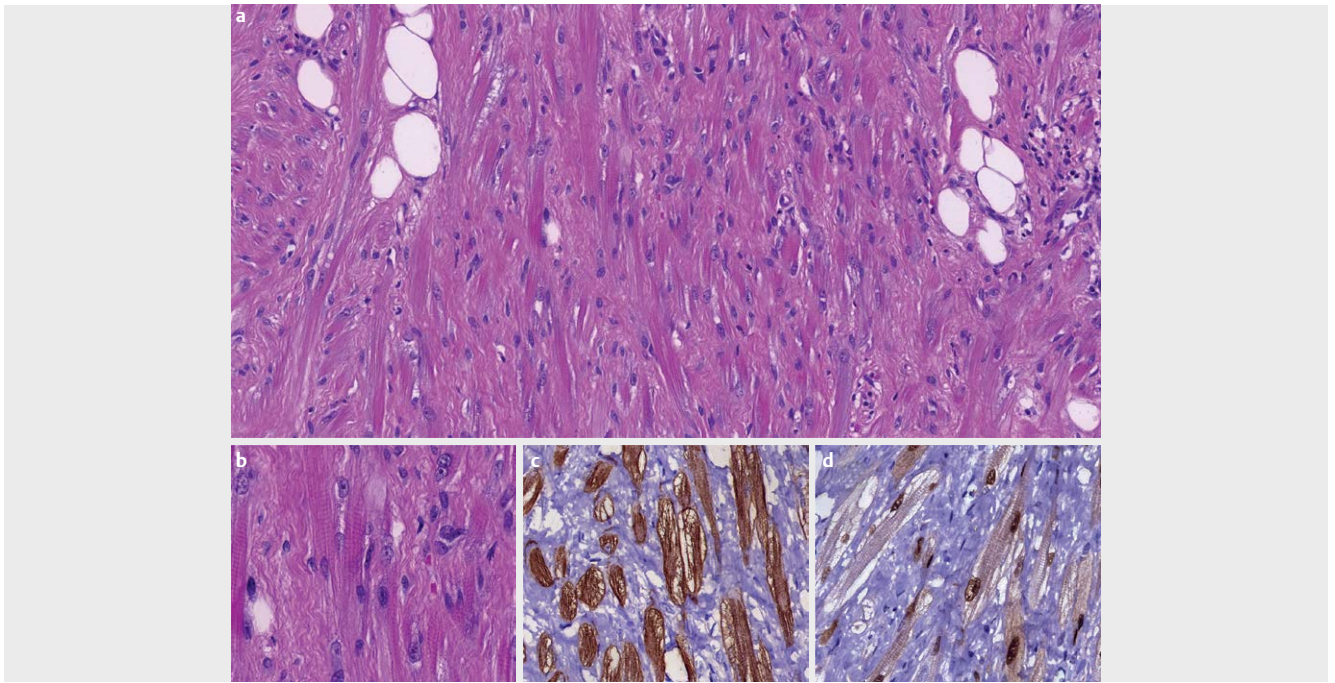
Note: Laryngeal rhabdomyomas mostly originate from the M. vocalis.

4.2.4 Paragangliomas

In the literature, 67 publications with 77 described cases of paragangliomas of the larynx are found.

Clinical manifestation

In most cases, paragangliomas are benign neuroendocrine tumors of the extra-adrenal chromaffin tissue of the autonomous neuro-

▶ **Fig. 6** Rhabdomyoma. **a** Histology reveals a tumor with large polygonal long cells with abundant granular eosinophilic cytoplasm which is partly striated and small round nuclei with distinct cell borders. Mitoses only rarely occur or are completely missing. **b** In higher amplification, a striation of the tumor cells is seen. **c** Immunohistochemistry reveals a high expression of desmin. **d** Myogenin reacts positively in single nuclei.

nal system. Laryngeal paraganglioma cells are mainly found in the supraglottic (90 %) or subglottic area and are associated with the superior and inferior laryngeal nerves. They make up 0.6 % of all laryngeal tumors [131]. The functional complaints depend on the size and the location. Mostly, the lesions are monofocal, rarely multi-local development is observed [132]. Paragangliomas may also appear in the trachea. Often the tumors are painful.

Diagnostics

Generally, biopsy is performed to classify the tumor. Hereby, smaller tumors are already completely removed. More often, the findings are large so that definitive resection has to be performed. Biopsies may lead to intensive hemorrhage. Histologically, paragangliomas have an alveolar basic structure; they are composed of cell accumulations that are kept together by fiber networks and are located in a well vascularized stroma. Immunohistochemistry confirms the diagnosis by presentation of chromogranin, synaptophysin, and neuron-specific enolase, in the supporting cells S100 protein is found [67]. After biopsy, a comprehensive staging should be performed. Beside MRI and CT scan, also methods of nuclear medicine may be applied due to the frequently expressed somatostatin receptors, e. g. DOTATATE PET which additionally allows exclusion of multilocal paragangliomas [131]. In the last years, several gene alterations could be identified that are responsible for the genesis of paragangliomas of the head and neck. The predominant signaling pathways concern the enzyme succinate-dehydrogenase (SDH) which consists of the five subunits of SDH-A, SDH-B, SDH-C, SDH-D, and SDH-AF2. Alterations in each of these five subunits lead to SDH deficient tumors, respectively defined as paraganglioma syndrome 1–5 [133]. Laryngeal manifestations have only been described for the paraganglioma type 1 (SDH-D). According changes are located on the locus 11q23.1 [133, 134]. Within a European registry (Head and Neck Paraganglioma Registry) different mutation subgroups of 121 paraganglioma-patients have been collected and statistically evaluated [135].

Therapy

The therapy of choice is surgery. Frequently, open approaches are described, e. g. via lateral pharyngotomy or thyrofissure. Naik et al. report about preoperative superselective embolization of the superior thyroid artery with subsequent partial laryngeal resection via lateral pharyngotomy including tracheostomy [136]. In addition, transoral laser surgical procedures are performed [137]. In the literature, successful primary radiotherapy is reported [138]. Pharmacotherapeutic approaches with octreotide (Sandostatin e. g. Kohlpharma GmbH, Merzig, Germany) may be applied for symptom reduction and stabilization of the course, especially in non-resectable lesions with positive initial octreotide scintigraphy [139].

Prognosis

In about 15 % of the cases, recurrences occur. In this context, rarely appearing malignant degeneration must be assumed [140]. Long-term follow-up is essential.
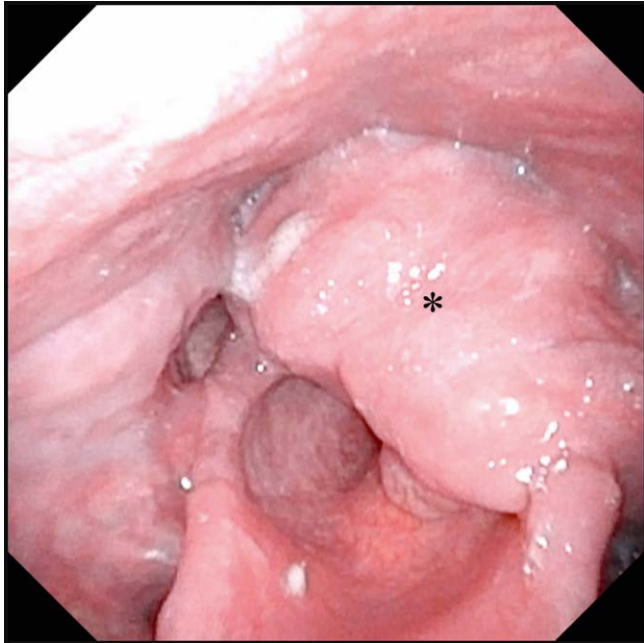
Note: Paragangliomas may cause pain. A nuclear-medical staging is recommended. The therapy of choice is surgery; however, high risk of tumor hemorrhage must be taken into consideration.

4.2.5 Schwannomas

In the literature, 82 publications on laryngeal schwannomas are found.

Clinical manifestation

Schwannomas, also called neurilemmomas (formerly: neurino-mas), belong to the group of neurogenic tumors. They originate from Schwann cells. Schwannomas occur frequently in the head and neck region, howe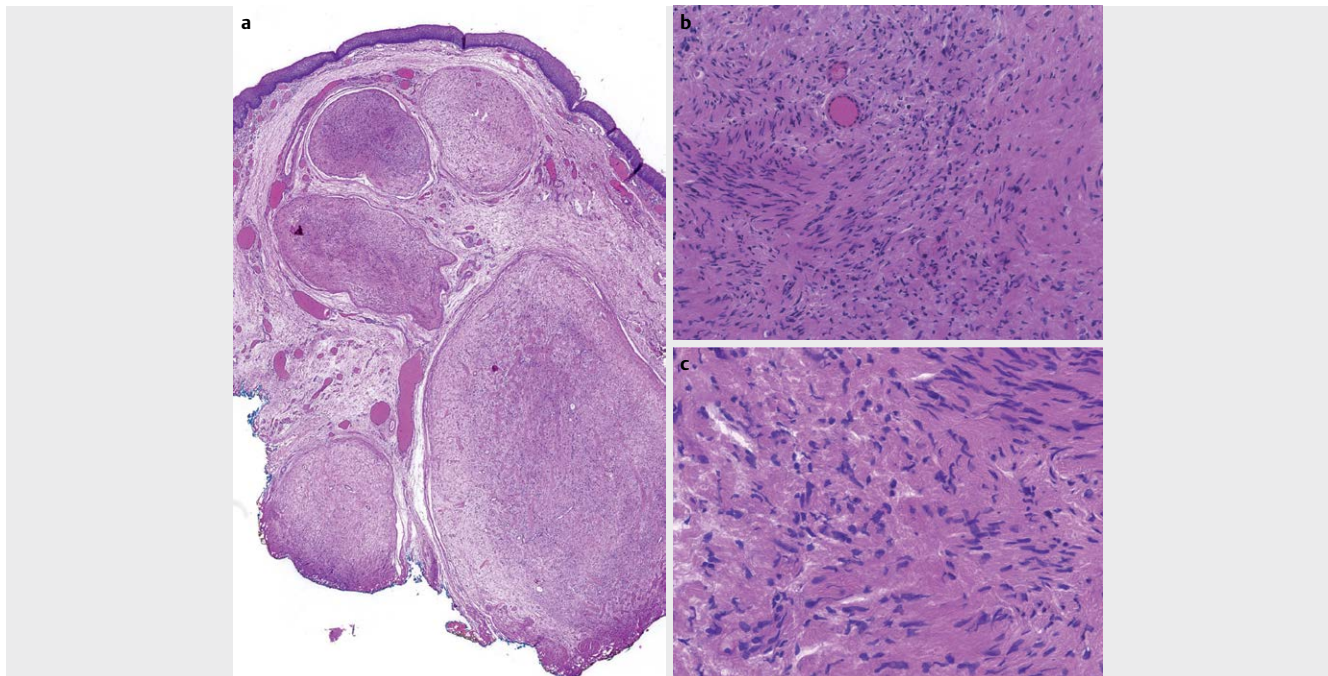ver, the larynx is very rarely affected. In the literature, more female patients with laryngeal schwannomas are mentioned compared to males. Generally the middle age groups are concerned. Rarely, laryngeal schwannomas are found in children [141]. Within the larynx, they develop in different locations [142, 143], e. g. (most frequently) at the aryepiglottic fold and the arytenoid region (▶ Fig. 7) [144], in the pre-epiglottic space [145], in the paraglottic space [146], at the false vocal cords, the vocal folds, the epiglottis, and in the subglottis. Schwannomas may also appear in the tracheal lumen. The origin are branches of the superior as well as inferior laryngeal nerve. The complaints depend on the size and location: Frequently Schwannomas are incidentally detected in the context of neck imaging.

Diagnostics

In the preoperative diagnostics, MRI is most important with a hyperintense signal in T2 and contrast enhancement for which T1 scan is chosen due to the poor native signal. Careful phoniatric functional diagnostics are required unless the mobility can be assessed based on the tumor mass. Finally, only histological and immuno-histochemical examinations can confirm the suspicion. Histologically, vertically and plait-like arranged fusiform cells with palisade structure of the nuclei are observed. Also in the larynx, two architectural types of Antoni A (compact with vertical palisades) and Antoni B (loosely myxomatous) are differentiated. In schwannomas as well as neurofibromas, the marker constellation of CD34 (-), SMA (-), S-100 (+) is typical (▶ Fig. 8). Hereby, the immunohistological identification of S-100 protein refers to a neurogenic origin. However, this is not absolutely specific.

▶ **Fig. 7** Schwannoma. (*) Plexiform laryngeal schwannoma of the left supraglottis; flexible laryngoscopy (chip/tip).

▶ **Fig. 8** Schwannoma. The figures show a plexiform schwannoma. **a** Schwannomas are nerve sheath tumors that consist entirely or nearly entirely of differentiated neoplastic Schwann cells. In the overview, a characteristic nodular growth is observed that is typical for plexiform schwannomas. **b/c** In higher amplification, a monotone, cell-rich spindle-cell tumor without atypia, necrosis or increased mitotic activity as indication of a benign tumor is seen in contrast to classic schwannomas, that have a growth pattern changing between Antoni **a** and **a**.

Therapy

Schwannomas are frequently detected as incidental findings in the context of neck imaging. In cases of absent functional disorders, first wait-and-scan strategy may be pursued after histological confirmation. Otherwise, therapy of choice is the surgical removal mostly via transoral microsurgery [143] but also via open approaches, partly with tracheostomy [145]. In the recent literature, reports on transoral robotic removal with the DaVinci system are found [119, 147].

Prognosis

In the literature, 5 cases with recurrences have been described. In general, postoperative sensible deficits or (depending on the origin of the schwannoma) also motor deficits are observed. Therefore, follow-up by phoniatricians is recommended.

Note: Schwannomas are mostly found at the aryepiglottic folds, however, they may occur in all areas of the larynx.

4.2.6 Neurofibromas

In the literature, 51 publications on neurofibromas of the larynx are found, some of them published as case series. 63 pediatric cases have been described up to now.

Clinical manifestation

Neurofibromas are neurogenic tumors with a predominantly fibrous part that originate from the endoneurium. Histologically the difference is made between simple, cell-rich, and plexiform neurofibromas. Manifestations in the larynx mostly occur in the context of generalized neurofibromatosis in the sense of von Recklinghausen's disease (neurofibromatosis [NF] I) [148, 149]. Especially hereby, the disease mainly manifests in (small) children. However, also isolated laryngeal manifestations have been described. Neurofibromas make up 0.05 % of all benign laryngeal tumors [150]. The clinical appearance depends on the size and the location of the findings. Comparable to schwannomas, neurofibromas are mostly found in the supraglottis and rarely in the subglottis or in the trachea [151].

Diagnostics

MRI is the imaging procedure of choice. Neurofibromas are hyperintense in T2 with central intermediary areas, in T1 weighting they have a weak to moderate signal. A clear differentiation with schwannomas is not always possible. However, MRI may frequently differentiate between plexiform tumors without clear borders and non-plexiform well-defined subtypes [153]. The immunohistological marker combination of neurofibromas is similar to the one of schwannomas.

Therapy

Similar to schwannomas, also here the wait-and-scan strategy is an option that should be interdisciplinarily discussed. Modern therapeutic procedures focus on endoscopic transoral resection or partial resection [154]. Especially plexiform neurofibromas are particularly poorly delimited and thus difficult to resect [149]. In the literature, there is no case where recurrence has not occurred, even after total laryngectomy. Therefore, the tendency is clearly to leave radical resections and to focus on function preserving (partial) re-

sections with clinical and imaging controls. Tracheostomy should be avoided as long as possible [155].

Prognosis

Because of the frequent recurrences even after radical surgeries, conservative surgical procedures are indicated, in cases of doubt also in the sense of partial resections. Therefore, the patients have to undergo long-term follow-up, regular MRI controls are necessary. Furthermore, the possibility of malignant degeneration must be taken into account.

Note: Laryngeal neurofibromas usually appear in the context of generalized neurofibromatosis and only rarely as isolated disease.
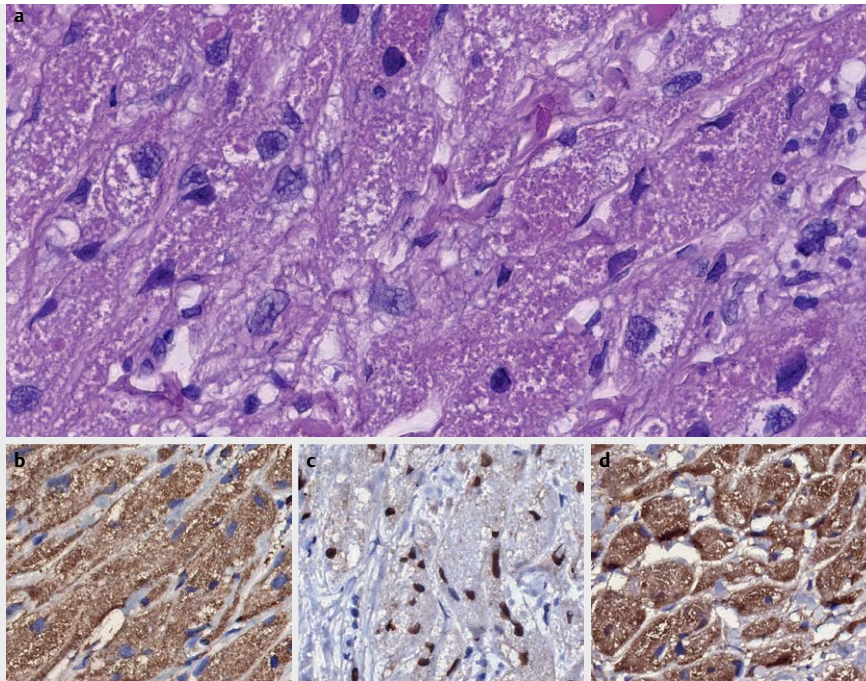
4.2.7 Granular cell tumors

In the literature, 76 publications are found on this topic with about 100 cases.

Clinical manifestation

Granular cell tumors belong to the tumors of neuroectodermal origin, they originate from Schwann cells. The oral cavity and in particular the tongue are most frequently affected, about 10 % of the head and neck manifestations concern the larynx [156]. Children as well as adults develop granular cell tumors, the gender distribution is balanced [157]. The predilection site within the larynx is the posterior part of the vocal folds (▶Fig. 9) [158]. The tumors impose as pale, submucously growing mass on the vocal folds, the initial symptom is dysphonia [159]. In 5 % of the cases, several laryngeal manifestations are observed [160]. Granular cell tumors also appear in the trachea, hereby the female gender is more frequently affected. Typically, these tumors affect the cervical parts of the trachea.
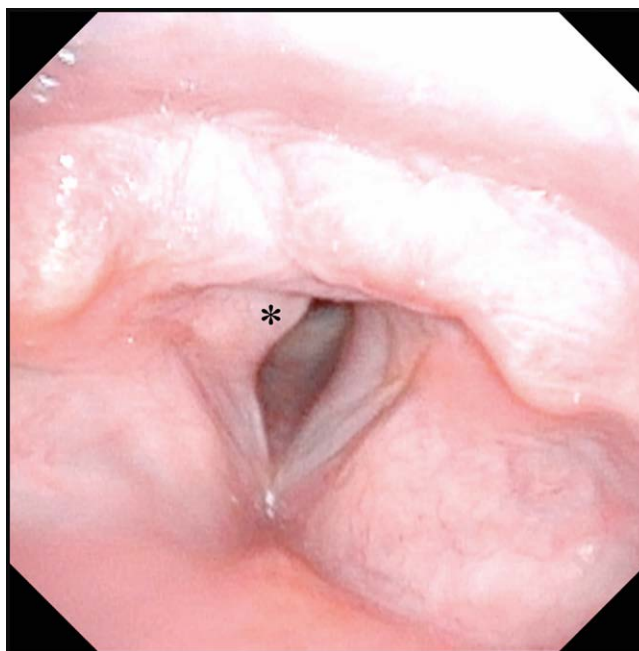
▶ **Fig. 9** Granular cell tumor. (*) Granular cell tumor of the posterior third of the right vocal fold; flexible laryngoscopy (chip/tip).

▶ **Fig. 10** Granular cell tumor. **a** Microscopic examination shows a tumor that has grown in large accumulations with large tumor cells that are not sharply defined and have a granular cytoplasm. The nuclei are mostly centrally located with homogenous, slightly hyperchromatic and enlarged vesicular nuclei. In immunohistochemistry, the tumor cells react positively on **b** S100 and **c** S0X10 as indication for neuroectodermal origin. **d** Furthermore, tumor cells react positively on CD68.

Diagnostics

The diagnosis can exclusively be made by histological and immunohistological examinations because the clinical picture is unspecific and the tumor rather reminds of a cyst. Submucously growing, polygonal, granular cells are typical, they react positive on S-100, CD 57, CD 68, and SOX 10 [161]. The S-100 positivity is typical for neurogenic tumors (▶ **Fig. 10**).

Therapy

Usually, the tumors are excised transorally by laser surgery [160, 162]. In rare subglottic affection, open surgical procedures should be preferred [163].

Prognosis

The prognosis after complete excision is good with a recurrence rate of 2–3 %. For granular cell tumors, malignant degeneration rates of 1–2 % are described. However, in the literature exists only one report about laryngeal malignant transformation [164].

Note: Granular cell tumors look like cysts, the suspected diagnosis could be made due to the uncommon location in the posterior third of the vocal folds.

4.2.8 Hemangiomas

In the literature, more than 300 publications are found on hemangiomas of the larynx.

Clinical manifestation

Laryngeal hemangiomas appear as cavernous and capillary lesions. In adults, mostly cavernous, in newborns and children capillary heman-
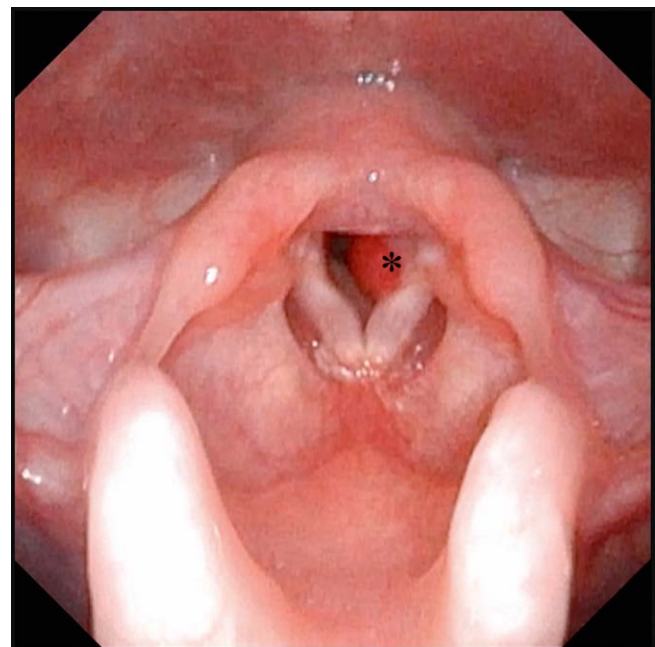
▶ **Fig. 11** Hemangioma. (*) Congenital subglottic hemangioma on the left with multiple midline hemangiomas; flexible laryngoscopy (chip/tip).

giomas are observed. Pediatric hemangiomas are significantly more frequent and classically located in the subglottis (▶ **Fig. 11**). Girls are more frequently affected than boys. Hemangiomas in adults occur more rarely and are located mainly in the supraglottis [165]. Macro-

scopically, hemangiomas appear as convex blue-reddish swellings with broad base that are covered by mucosa, sometimes also as pedicled polyps with smooth or rough surface. In dependence of the tumor location, the patients become symptomatic in cases of subglottic findings, predominantly due to inspiratory stridor, cough, and rapid oxygen desaturation [166]. While pediatric hemangiomas grow within the first months of life, involution is observed around the first birthday [167]. Hemangiomas may also appear in the trachea.

Diagnostics

Beside endoscopic examination, imaging plays a major role. Typical findings in MRI are the asymmetric stenosis of the subglottic airways in the coronary imaging. MRI is the imaging procedure of choice. Hemangiomas impose as solid tumors of moderate intensity in T1w as well as hyperintense in T2 weighting. Flow-voids are typical for shunt formations [168]. Histological diagnostics are not always easy, the glucose carrier protein 1 may be used as immunohistological marker for infantile hemangiomas.

Therapy

In the literature, different therapy options are discussed for subglottic hemangiomas. Most decisive is the extent of the subglottic lumen stenosis. In cases of minor stenosis, a conservative procedure (watch-and-wait) is suggested, regular follow-up examinations are necessary. In cases of moderate lumen stenosis up to 50%, corticosteroids are recommended. If the stenosis is higher up to 70%, laser treatment is the therapy of choice. In the literature cutting and angiolytic laser modalities are described (CO_2, KTP, and Nd:YAG laser) [167]. Tracheostomy is recommended as emergency measure in cases of large findings or multi-local lesions. Open surgical excisions are reserved to extended subglottic findings with lumen stenosis of more than 70%. Reconstruction (e. g. with rib cartilage) should be included in the planning. There are several pharmacotherapeutic approaches (e. g. interferon or vincristine). The strategy of radiotherapy was abandoned several decades ago, also cryotherapy is no longer recommended. As acute measure, the treatment with propranolol for several months is suitable. Application of beta blockers seems to be effective mostly in children and is often used as primary therapy [169, 170].

Note: Predilection site for pediatric laryngeal hemangiomas is the subglottis. By means of MRI the diagnosis can often be verified. The decision for therapy depends on the extent of the subglottic lumen stenosis.

5 Rare malignant tumors

The current incidence, prevalence, and mortality of laryngeal cancer are estimated to be 2.76 cases/year per 100,000 population, 14.33 cases per 100,000 population, and 1.66 deaths/year per 100,000 population, respectively [171]. Squamous cell carcinomas are clearly the most frequent entity, with only 5% of cases being rare epithelial and non-epithelial laryngeal malignancies. In the following, some entities will be exemplarily highlighted in more detail.

5.1 Carcinomas

5.1.1 Laryngeal adeno-squamous carcinomas (LASC)

A literature research reveals 31 publications. Up to now, about 100 cases have been described in the upper aerodigestive tract [172].

Clinical manifestation

Adeno-squamous carcinoma is an extremely rare and highly aggressive malignancy. The larynx is the most frequent manifestation site [173]. Risk factors include nicotine and alcohol consumption. An association with high-risk types of human papillomavirus has been discussed, however, it seems to be improbable [174, 175]. The disease usually occurs in an advanced age, while men are clearly more frequently affected with a ratio of 4:1. The symptoms depend on the exact location and the extent of the carcinoma and tend to be non-specific. Locoregional lymph node metastasis occurs in 75% of the cases; at the time of initial diagnosis, 25% of the patients already have distant metastases, mainly in the lung [176].

Diagnostics

In addition to clinical examination and panendoscopy with biopsy, imaging techniques such as CT and MRI are indicated. The histological verification may be difficult, because the carcinoma often grows submucously and may thus be overlooked in early stages. Characteristic histology is the biphasic morphology of the tumor with squamous and cribriform tubulo-glandular differentiation in close proximity. Intraluminal accumulation of mucin is a typical finding as well. Histomorphologically, the differentiation with mucoepidermoid carcinoma is difficult; therefore additional immunohistochemical examinations are necessary. In this context, detection of p63, carcino-embryonic antigen as well as low- and high-molecular cytokeratin (CK) can be performed. CK20 is negative [177]. Reliable differentiation from mucoepidermoid carcinoma and conventional squamous cell carcinoma is important because LASC has a significantly poorer prognosis. A publication by Yoshimura and colleagues revealed that biopsies from oral ASC were frequently misinterpreted [178].

Therapy

There is no clear consensus regarding an adequate therapy for LASC. Depending on the tumor size, it includes often radical surgery with consideration of the lymphatic drainage, followed by adjuvant radiotherapy with or without chemotherapy.

Prognosis

The disease has a significantly worse prognosis than conventional squamous cell carcinoma, with a 5-year survival rate of only 13–25%. Causes of death are local recurrences as well as distant metastases. Beside the aggressive growth behavior of the tumor, potential histological misinterpretations with resulting incorrect therapy concepts also contribute to the poor prognosis. An early diagnosis allows the introduction of adequate therapy and is prognostically relevant [173].

Note: Adeno-squamous carcinomas have a poor prognosis; differentiation from mucoepidermoid carcinomas or squamous cell carcinomas is only possible by immunohistochemistry.

5.1.2 Laryngeal lymphoepithelial carcinomas (LLEC)

With 0.2% of all laryngeal tumors, this carcinoma is extremely rare. Up to now, in the literature, only 40 cases have been described [179, 180].

Clinical manifestation

Lymphoepithelial carcinomas are Epstein-Barr virus (EBV)-associated tumors that are located mainly in the nasopharynx and have an endemic geographic distribution, particularly in Southeast Asia [181, 182]. In comparison to nasopharyngeal manifestation, LLEC is very rare. An EBV association is controversially discussed, in any case it seems to be significantly lower than in the nasopharynx. The carcinoma is frequently located in the supraglottis, rarely subglottic or in the trachea [183]. With a ratio of 3:1, men are more frequently affected than women, preferentially between the 5th and 7th decade of life [182]. In contrast to lymphoepithelial nasopharyngeal carcinomas, LLEC less commonly affect Caucasians. The clinical symptoms are non-specific [184].

Diagnostics

In addition to clinical examination and panendoscopy including biopsy, also CT and/or MRI are necessary for therapy planning, similar to all other laryngeal tumors. Predominantly submucosal growth makes tumor detection difficult, especially in early stages, as well as adequate specimen collection and to treatment planning. Often cervical lymph node metastases represent the initial symptom so that diagnosis is made by lymph node biopsy, initially suggesting nasopharyngeal carcinoma. An EBV association is investigated by means of in situ hybridization. In this context, the identification of EBV encoded small RNA (EBER) is confirmatory. Important further differential diagnoses are Non-Hodgkin-Lymphomas, undifferentiated carcinomas, and malignant melanomas [179, 185]. Furthermore, laryngeal metastasis of a nasopharyngeal carcinoma have to be excluded.

Therapy

LLEC is highly radiosensitive, similar to lymphoepithelial carcinoma of the nasopharynx, making radiotherapy the treatment of choice. It ensures good local tumor control [186, 187]. Due to the frequent presence of extensive locoregional metastases, irradiation of the lymphatic drainage area is always necessary. The role of chemotherapy is not yet fully clarified, however, it is assumed that concomitant chemotherapy may reduce the rate of distant metastases [182, 187, 188].

Prognosis

About one-third of LLEC patients die as a result of their disease, mostly due to distant metastases [182, 189].

Note: The lymphoepithelial laryngeal carcinoma is treated primarily by radiotherapy.

5.1.3 Adenoid cystic carcinoma of the larynx

In the literature, more than 200 articles have been published on adenoid cystic carcinomas of the larynx. Most articles are reports that describe several cases.

Clinical manifestation

Adenoid cystic carcinoma (ACC) are the most frequent tumors of the minor salivary glands. The density of minor salivary glands within the laryngeal mucosa is 23–47 glands/cm^2, approximately 20–40 fold lower than in the oral cavity [190]. This is one reason for the rarity of laryngeal ACC with <1% of all laryngeal tumors.

ACC are nearly equally found in both genders with a mean age of about 50 years [191, 192]. The most frequent location is the subglottis (▶ Fig. 12) with extension into the trachea [193, 194]. ACC of the supraglottis and the level of the vocal folds is very rare. Depending on the location, symptoms like globus sensation, hoarseness, dyspnea, and stridor may occur. The tumors grow very slowly, therefore the symptoms also develop with a corresponding delay. . A clear risk factor for the development of ACC could not be identified up to now. Cervical lymph node metastases accur very rarely, distant metastases, particularly pulmonary metastases, may manifest after many years in analogy to ACC of other locations [195, 196].

Diagnostics

Cross-sectional imaging diagnostics are necessary for definition of the tumor size and therapy planning. However, it must be taken into consideration that the extent is often underestimated due to the diffuse submucosal tumor growth and frequent presence of perineural sheath infiltration. Confirmation is provided by histological and immunohistological examinations. ACC show numerous tubular and cribriform structures. Perineural sheath infiltration is ubiquitous. Immunohistochemical markers are KIT (CD117) in the inner epithelial cells and p63 as well as SMA in the peripheral myoepithelial cells. Furthermore, staining for MYB and MYB/NFIB is performed [197]. Significant genetic alteration is a t(6;9) chromosome translocation or rarely a t(8;9) translocation. The resulting fusions involve the MYB or MYBL1 oncogene and the transcription factor gene NFIB (▶ Fig. 13).

Therapy and prognosis

Due to the relatively low radiosensitivity of these tumors, surgery must be considered as the therapy of choice. Because of the above-mentioned growth pattern, a radical procedure possibly in the sense of total laryngectomy is required, although even radical surgery often results in R1 situations with regard to perineural sheath infiltration [190 198, 199]. Despite ACC showing relative radioresistance, some trials could reveal an improved local and locoregional tumor control by means of adjuvant radiotherapy in R1 situations [200–202]. Chen and colleagues reported that local tumor control in patients with ACC in the head and neck region at 5 and 10 years with adjuvant therapy was 92 and 84%, respectively, and without radiotherapy 80 and 61%, respectively [203]. In addition to IMRT (e. g. 50 Gy), heavy ion radiation may improve the prognosis [204].

Prognosis

Factors determining the prognosis are the resection status, tumor size, and the perineural sheath infiltration [205]. The 5-year survival rate of patients with laryngeal ACC ranges from 43 to 75% [206–208]. The high difference can be explained by the low number of cases. In general, the local tumor control rate is good due to radical surgery with adjuvant radiation, if needed, the patients die almost exclusively due to distant metastases.

Note: Surgical approaches are the therapy of choice for adenoid cystic carcinomas of the larynx. The prognosis is determined by late distant metastasis.

5.1.4 Mucoepidermoid carcinomas (MEC)

There are only about 100 case reports on this tumor entity.

Clinical manifestation

The symptoms of MEC are similar to those of other tumors in the larynx. The tumors are found supraglottically as well as subglottically [209]. There is one report of a 12-year-old child with the disease, but typically adults are affected [210].
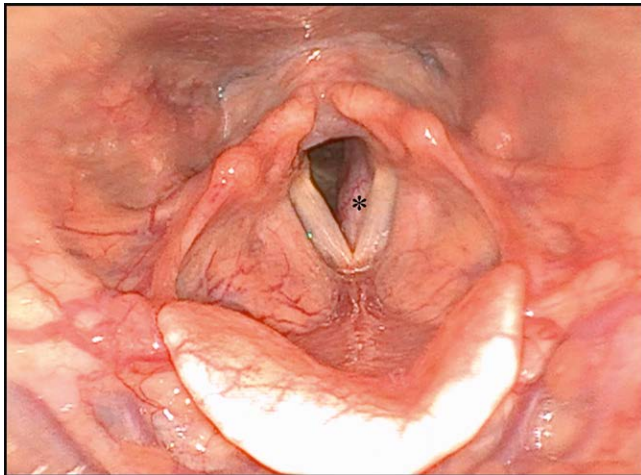
▶ **Fig. 12** Adenoid cystic carcinoma. (*) Adenoid cystic carcinoma of the left subglottis; flexible laryngoscopy (chip/tip).

Diagnostics

In addition to clinical examination and panendoscopy including biopsy, imaging procedures such as CT and/or MRI are indicated. Diagnosis is made by histologic confirmation. The evaluation can be very challenging; there is a risk of misidentification of the tumor with e. g. squamous cell carcinoma, adenocarcinoma, adenosquamous cell carcinoma, or neuroendocrine carcinoma [211]. MEC consist of three cell types: epidermoid cells, mucous secreting cells, and intermediary cells. Histologically, a differentiation between low-grade (low-malignant), intermediate-grade (intermediate-grade malignant), and high-grade (highly malignant) types is performed.

Therapy

The therapeutic procedures are based on the treatment of MEC of the salivary glands. Predominantly, surgery is performed with frequently subsequent adjuvant radiation, if required in combination with chemotherapy.

Prognosis

The differentiation is one of the most important prognostic factors of MEC. Low- and intermediate-grade tumors have a good prognosis after adequate surgical resection with 10-year survival rates of 90 % and 70 %, respectively. High-grade tumors, however, have a 10-year survival rate of only 25 %. In cases of well-differentiated, small, and non-metastasized tumors, a close follow-up concept may be performed instead of adjuvant therapy [212, 213].

Note: The prognosis of MEC of the larynx depends on the grade of differentiation.
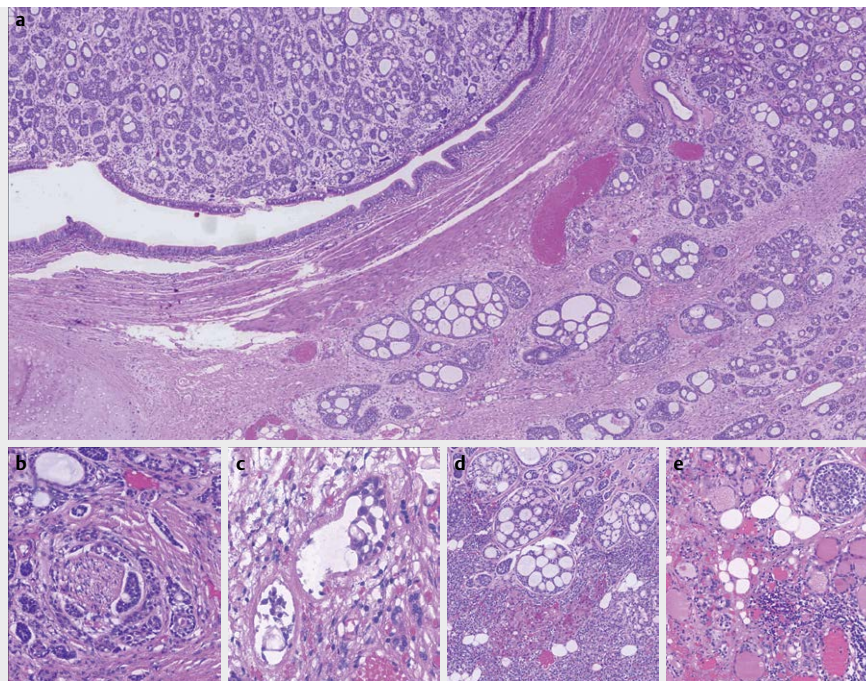
▶ **Fig. 13** Adenoid cystic carcinoma. **a** The adenoid cystic carcinoma is a salivary gland carcinoma consisting of epithelial and myoepithelial cells and showing a characteristic tubular, cribriform and solid growth. In the tumor glands, often an amorphous basophilic matrix is found. Due to the typical morphology, the diagnosis is mostly possible with conventional morphological preparation. Extended tumor infiltrates are seen under the laryngeal mucosa. The carcinoma develops perineural sheath infiltration (see **b**) and lymphangiosis carcinomatosa (see **c**). Furthermore, an infiltration of the parathyroid gland (**d**) and the thyroid gland is revealed.

5.1.5 Neuroendocrine carcinomas of the larynx (NEC-L)

NEC-L represent a group of rare neuroendocrine carcinomas of the head and neck. In the literature, about 500 cases have been described.

Clinical manifestation

In analogy to NECs of other locations such as the lung, 3 different subtypes are distinguished in the larynx: well-differentiated (G1) NEC-L (synonym: carcinoid), moderately differentiated (G2) NEC-L (synonym: atypical carcinoid), and poorly differentiated (G3) NEC-L, which in turn is subdivided into small-cell (sm) and large cell (lc) types [214]. The G1 NEC-L occurs most rarely, followed by G3 type, whereas the G2 NEC-L appears most frequently. This distinction has therapeutic consequences, as clinical behavior and response to treatment differ significantly between the subtypes.

NEC-L concerns mostly the male gender with a sex ratio of 3:1, except of well-differentiated NEC-L in which no sex preference has been observed [214, 215]. The disease peak is in the 5th decade of life and frequently a history of tobacco abuse is found. The most frequent location is the supraglottis. NEC-L causes non-specific symptoms such as hoarseness, dysphagia, or sore throat. In very rare cases, a paraneoplastic syndrome may appear due to tumor-induced hormone overproduction [216]. Of particular note is the high tendency of NEC-L to metastasize dermally, which is observed in up to 20% of the cases, according to the literature [217–219]. Therefore, a careful inspection of the skin is urgently required in the context of staging.

Diagnostics

In addition to the clinical examination including panendoscopy with biopsy, different diagnostic procedures are applied. Imaging techniques include ultrasound, CT as well as PET-CT (FDG-PET-CT/DO-TATE-PET-CT)[220]. Regarding immunohistological diagnostics, different markers are assessed such as cytokeratin, EMA, and at least one positive neuroendocrine marker (e. g. chromogranin A, synaptophysin, neural cell adhesion molecule NCAM (CD56)) [221]. NEC can secrete various hormones such as serotonin, calcitonin, growth hormones, insulin, gastrin, or glucagon. To evaluate the prognosis of the patient, Ki 67 expression analysis is obligatory.

Medullary thyroid carcinoma should be taken into consideration as differential diagnosis and excluded especially in cases of increased serum calcitonin levels that appear mainly in G2 NEC-L [218]. Further, NEC-L has to be delineated from laryngeal metastasis of a NEC of other origin (e. g. lung).

Therapy

Therapeutic decisions should be made primarily interdisciplinarily and subtype-specific. In cases of G1 NEC-L, local resection in the sense of either open or transoral endoscopic laser surgical partial laryngectomy is recommended. G2 NEC-L are the largest subgroup. Therapy planning is challenging because 30% of the patients already have distant metastases at the time of first presentation. Radical surgical resection is indicated. Elective neck dissection should be performed, often occult metastases are found. The sensitivity of G2 NEC-L to radiotherapy is questionable. It could be shown that patients who underwent primary radiotherapy had a lower disease-specific survival compared to patients that have been treated sur-

gically. Recurrences can occur even after 5 years of conventional follow-up period, so that follow-up should be extended to 10 years. Patients with G3 sm- and lc-NEC-L develop early distant metastases. In these cases, the treatment is similar to that of neuroendocrine lung carcinomas and consists of a combination of radiotherapy and chemotherapy [215].

Prognosis

The course of the disease mainly depends on the differentiation grade. The recurrence rate amounts to 35% for G1 NEC-L and 81% for lc-NEC-L. Patients with a G2 or G3 lc-NEC-L develop more frequently distant metastases compared to patients with G1 NEC-L [215]. The disease-free survival (DFS) after 5 years of G1 NEC-L amounts to 80%. In contrast, the 5-year DFS for G2, G3 sm-NEC-L and lc-NEC-L is 52%, 19% and 15%, respectively [215].

Note: There are numerous neuroendocrine carcinomas. This confirms the necessity of interdisciplinary therapy planning. Due to the high proneness of NEC-L to dermal metastasis, a thorough inspection of the skin is essential.

5.2 Malignant non-epithelial tumors

About 4.3% of the sarcomas appear in the head and neck [222]. This heterogeneous group of diseases is characterized by a variety of histological and clinical presentations, making therapy planning challenging. In the larynx, sarcomas of the skeleton as well as soft tissue are found. J. Le Vay, B. O'Sullivan and colleagues investigated the prognosis for different types of head and neck sarcomas. They discovered that well-differentiated sarcomas and the subtypes of liposarcoma, fibrosarcoma, and chondrosarcoma are relatively slow-growing tumors with a low incidence of metastases. On the other hand, poorly differentiated and biologically aggressive tumors such as angiosarcoma, osteogenic sarcoma or neurofibrosarcoma show an increased tendency for distant metastasis [223, 224].

Chondrosarcomas occur most frequently as sarcomas of the skeletal system, whereas soft tissue sarcomas are extremely rare. In the following chapters, chondrosarcomas and rhabdomyosarcomas will be considered more in detail. Regarding the entities fibrosarcoma, liposarcoma, synovial sarcoma, angiosarcoma, and leiomyosarcoma, the authors refer to the literature on this topic.

5.2.1 Laryngeal chondrosarcoma

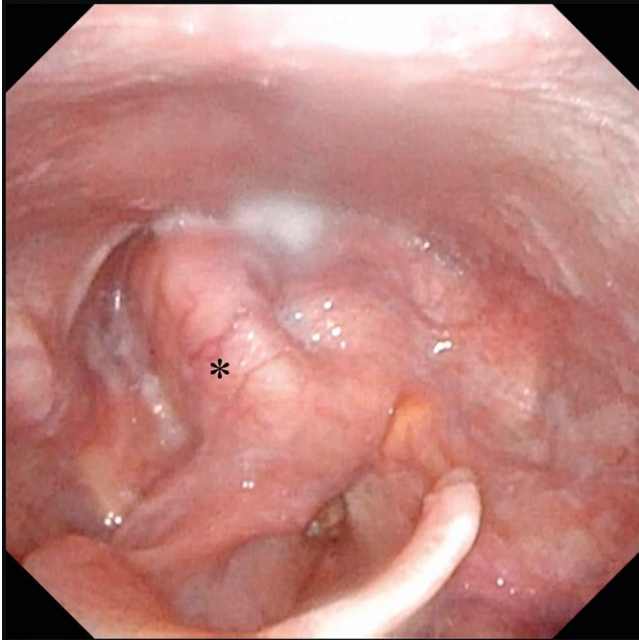In the literature, more than 300 publications are found on laryngeal chondrosarcomas, an estimation of the number of known cases is difficult.

Clinical manifestation

Laryngeal chondrosarcoma (LCS) is the most frequently appearing type of sarcoma in the larynx. After squamous cell carcinomas and adenocarcinomas, the chondrosarcoma is the third most common malignancy of the larynx. Chondrosarcomas are more frequent than chrondromas. The clinical symptoms are non-specific and do not vary from other laryngeal neoplasms. LCS metastasize locoregionally with a rate of 2% [225]. Distant metastases occur in about 8.5% of the cases, frequently, the lung and the bones are affected [226]. LCS mostly develops from hyaline cartilage of the cricoid (▶ Fig. 14) [227].

Diagnostics

The histological confirmation in the context of panendoscopy is essential for the diagnosis. Histologically, it is difficult to differentiate the most frequently occurring well-differentiated chrondrosarcomas from chondromas. The number of mitoses is decisive as well as the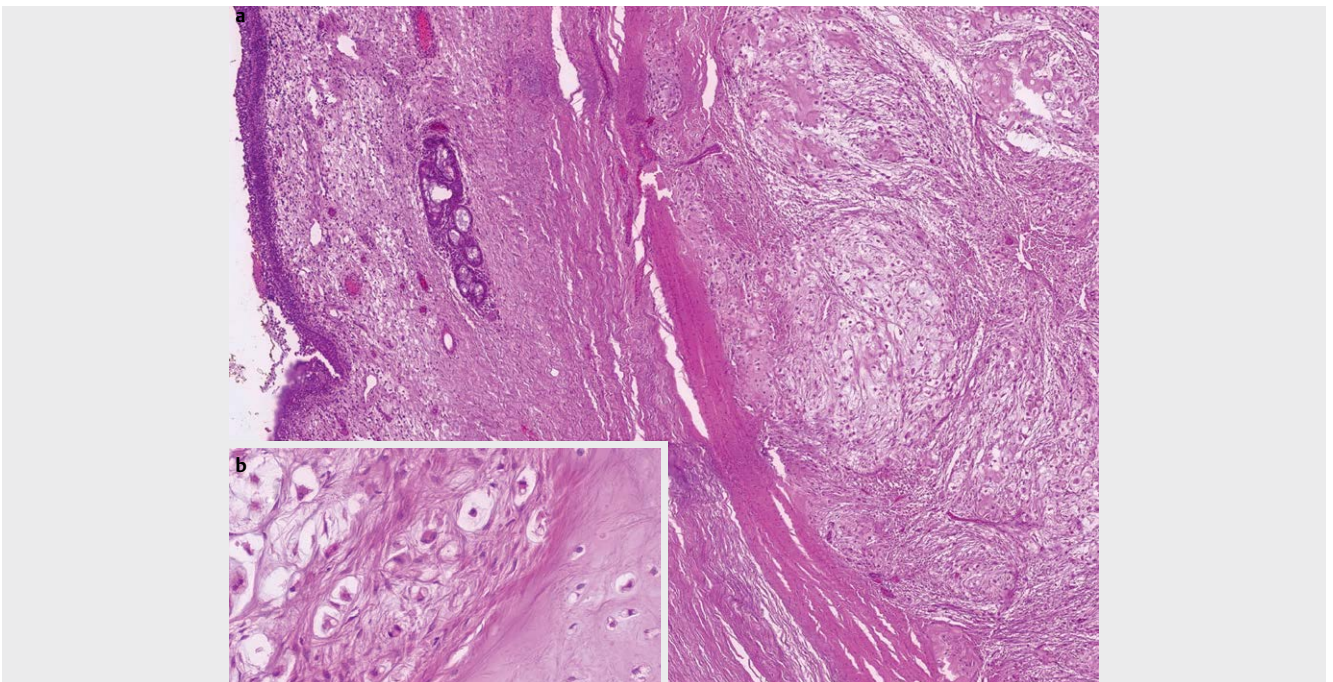 hypercellularity and nuclei pleomorphisms, and other anomalies of the nuclei (►Fig. 15). The infiltration of neighboring healthy cartilage or bone excludes chondroma and argues for sarcoma. Additional immunohistochemical examinations are performed to assess the mitotic activity. CT and MRI provide important information on the tumor extension and the adjacent healthy soft tissue.

Therapy

Surgery is the procedure of choice for treatment of LCS. The merely endoscopic resection has advantages under a functional aspect and due to the lower morbidity. However, regarding the decision in favor of endoscopic tumor resection it should be taken into account that the recurrence rate is very high at 50 % [228, 229]. In general, open surgical procedures are performed, ideally under microscopic control. Tracheostomies can frequently be avoided. One must keep in mind that the biopsy access in the context of definitive therapy has to be excised as well. This applies particularly for the accesses from outside. Because of the mostly slow growth of well differentiated subtypes, nowadays a radical surgical procedure is not performed. Moreover, organ preservation is in the focus, so that tumors are removed with a narrow safety under preservation of the mucosa and the function, followed by close MRI follow-up examinations. Recurrences can also be treated circumscribed surgical measures. Today, total laryngectomy is considered as ultima ratio.

Prognosis

In general, the prognosis is good. Dubal and colleagues performed a retrospective analysis of the tumor registry called SEER (United States National Cancer Institute's Surveillance, Epidemiology, and End Results). They recorded 143 cases with a median age of about

►**Fig. 14** Chondrosarcoma. (*) low-grade (G1) chondrosarcoma at the right arytenoid and cricoid; flexible laryngoscopy (chip/tip).

►**Fig. 15** Chondrosarcoma. **a** Chondrosarcomas of the larynx are malignant mesenchymal tumors of the hyaline cartilage. In the overview, a tumor with lobular structure and chrondroid matrix and increased cellularity is seen. The tumor is located under the laryngeal superficial epithelium. **b** In higher amplification, the nuclear pleomorphism and hyperchromatism of the neoplastic chondrocytes is displayed in contrast to non-neoplastic cartilaginous tissue (right side). There are also cartilaginous lacunae with two nuclei.

61 years. The male sex was most commonly affected, accounting for 76 %. Analysis of disease-specific survival showed 96.5 %, 88.6 %, and 84.8 % at 1, 5, and 10 years, respectively.

Note: The treatment of chondrosarcomas of the larynx frequently allows organ preservation. The tumors grow slowly and today surgery is no longer that radical. It must be taken into account that the biopsy access has to be excised in the context of definitive therapy as well.

5.2.2 Rhabdomyosarcoma

In the literature, about 100 articles are found on rhabdomyosarcomas of the larynx.

Clinical manifestation

Rhabdomyosarcomas (RMS) are mesenchymal tumors that originate from the striated muscles and belong to the group of soft tissue sarcomas. About one-third of RMS appear in the head and neck while the orbit, nasopharynx, and nose are the most frequently observed manifestation sites. The larynx is very rarely affected. According to the WHO, RMS are classified into three histological groups. They include embryonic RMS, alveolar RMS, and pleomorphic RMS. Embryonic RMS may affect children as well as adults [231]. Pleomorphic RMS exclusively appears in adults. The age distribution for RMS is as follows: 1 % at the age of < 1 year and 13 % for ≥ 15-year-old. Thus, the majority of the patients (> 85 %) is between 1 and 15 years old [232]. RMS affect mainly the glottis and supraglottis, and males are involved in more than 90 % of the cases. The symptoms are non-specific. Pleomorphic RMS is characterized by a highly malignant tumor biology.

Diagnostics

In addition to histological confirmation in the context of panendoscopy, imaging procedures (CT and MRI scan) are considered as standard procedures. The additional immunohistological examination is crucial. The identification of desmin and myogenin (MYF 4) is typical. Furthermore, the markers of MYOD1, fast myosin, myoglobin, MSA, and SMA can be verified (▶ **Fig. 16**). Especially the alveolar subtypes express also non-myogenic markers such as cytokeratin, EMA, CD 56, chromogranin, synaptophysin, CD 20, and CD 99. As a particularity, alveolar RMS have a PAX3-FOX01 gene fusion and their identification may be helpful in the context of differential diagnosis [233].

Therapy

Patients with RMS should be treated only in specialized centers. Pediatric patients are evaluated by the Cooperative Weichteilsarkom Studiengruppe (CWS; cooperative soft tisse sarcoma study group). Hereby, a guideline-conform treatment recommendation is made. According to Hicks and colleagues, chemotherapy is favored in all embryonic RMS consisting of vincristine and actinomycin D without radiotherapy. In unfavorable histological groups, among them alveolar, undifferentiated, and anaplastic types, cytoxan as well as radiotherapy are applied in addition to vincristine and actinomycin D [231]. In adults, surgery is the therapy of choice in cases of resectable tumors [234].

Prognosis

Patients with embryonic RMS have a good prognosis. The prognosis for alveolar RMS is poorer than for embryonic RMS. According to Kissane, pleomorphic RMS have the worst prognosis [231].
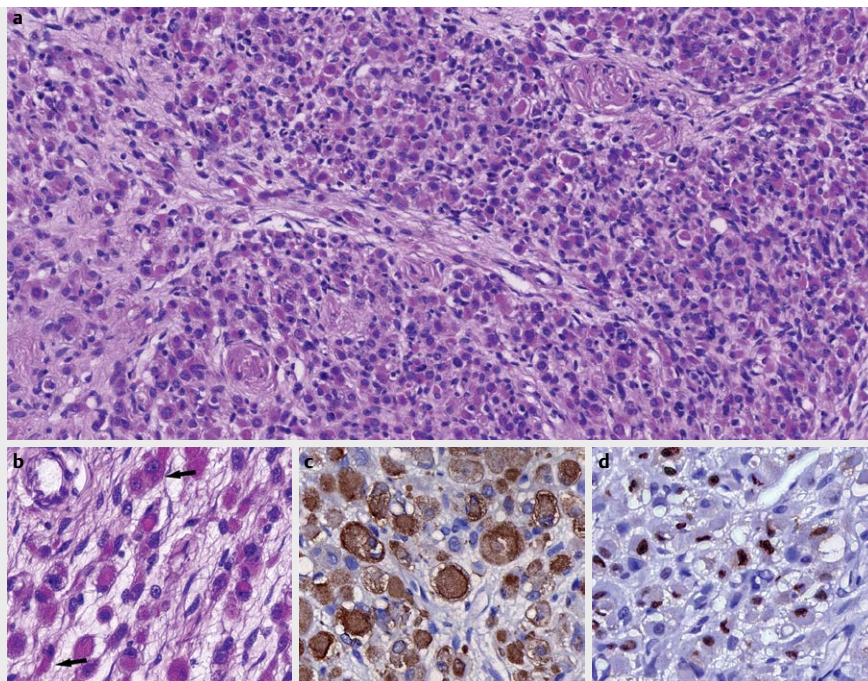
▶ **Fig. 16** Embryonic rhabdomyosarcoma. **a** The embryonic rhabdomyosarcoma is a malignant soft tissue tumor with morphological and immunophenotypical properties of embryonic skeleton muscles. Histologically predominantly differentiating rhabdomyoblasts develop with strongly eosinophilic and elongated cytoplasm that may be increasingly observed after previous therapy (such as in this case). The nuclei are clearly enlarged and hyperchromatic. **b** In higher amplification single tumor cells with multiple nuclei (arrow) and sporadic striation. **c** Immunohistochemically, the tumor cells react positively on desmin and myogenin.

Note: Therapy planning of the different types of rhabdomyosarcoma is performed in an interdisciplinary approach. Only for adults, the surgical treatment is in the fore.

6 Laryngeal and tracheal manifestations of general diseases

6.1 Rheumatoid arthritis (RA)

RA is an inflammatory chronic autoimmune disease with a prevalence of about 1 % that may lead to severe joint and bone damage. The progressive disease manifests frequently in the larynx, up to 75 % of the patients may develop voice disorders [235, 236].

Clinical manifestation

The primary symptom is dysphonia, which is caused by an affection of the cricoarytenoid joints. Furthermore, mucosal lesions of the vocal folds (e. g. nodules) and neurogenic muscle disorders may lead to a voice changes. Rarely, affected patients also report about pains during speech, chronic cough, or dyspnea in the cases of bilateral vocal fold fixations [237–240].

Diagnostics

In general, the underlying rheumatic disease of the patients is known, the diagnosis is thus made in the overall context. Structural changes can be documented by means of video-laryngostroboscopic examination. In the initial stages of the disease, rednes and swelling in the area of the arytenoid cartilages are typical signs, swollen mucosa of the vocal folds, especially in the posterior parts, develops only in the course of the disease. With progressive arytenoid fixation, the glottic gap becomes increasingly narrow. The differentiation is important between primary symptoms due to the disease and secondary symptoms due to immunosuppressive corticoid therapy. Arthritis-related impairment of the mobility of the laryngeal joints can be verified functionally in the context of microlaryngoscopy [241]. For differential diagnosis, it must be taken into account that beside RA also other systemic diseases may cause an affection of the cricothyroid and cricoarytenoid joint [242–244]. In high-resolution CT, joint changes may be detected very clearly. Hence, it is an integral component of diagnostics.

Therapy and prognosis

Mainly the treatment of the underlying disease is performed. Logopedic therapy can be offered as a supportive treatment. Steroids may be applied systemically or intralesionally [245, 246]. In cases of rheumatic vocal fold nodules, microsurgical treatment is recommended after failed conservative therapy.

Note: 75 % of all patients with rheumatoid arthritis develop laryngeal symptoms.

6.2 Primary laryngotracheal amyloidosis

Primary amyloidosis is a progressive systemic disease with deposits of insoluble protein fibers (amyloid) in the tissue. In Germany, primary amyloidosis occurs with an incidence of 6–10 cases per 1 000 000 inhabitants per year, 15 % of the cases are localized, while a small percentage of these cases affecting the larynx (PLA)

[247, 248]. In the head and neck, amyloid deposits also occur orally, pharyngeally, and in the paranasal sinuses. Only 400 cases of PLA have been described in the literature. In the context of primary amyloidosis, mostly light chain amyloid is deposited. At this point, it should be mentioned that secondary amyloidosis (on the basis of chronic infectious and non-infectious diseases, lymphatic tumors or long-term dialysis) appears significantly more frequently. Regarding the systemic type, different other amyloid types can be detected beside light chain amyloids.

Clinical manifestation

The disease progresses slowly. Depending on the location, different symptoms may occur. These include dysphagia, hoarseness, dyspnea, and stridor. Sometimes, the disease may be misdiagnosed as asthma or chronic obstructive bronchitis [249]. Clinically, often singular or multiple yellowish polypoid, submucous lesions are present (▶ **Fig. 17**). Mostly, the single foci do not exceed 1 cm in size. Young adults are most commonly affected. Predilection site is the supraglottis. Ulcerations may also occur focally.

Diagnosis

Clinical examination including phoniatric assessment, imaging procedures (CT and MRI scan) as well as panendoscopy with biopsy are indicated for diagnosis. The clinical findings are typical. The Congo red staining is an established technique for confirmation of amyloid deposits (▶ **Fig. 18**) [250]. A comprehensive examination is obligatory to exclude further amyloid deposits in the head and neck region, furthermore the causes of secondary amyloidosis must be investigated. For this purpose, bone marrow aspiration, blood and urine examinations are necessary to exclude a light chain disease, in particular plasmocytoma must be excluded as a cause. The University of Heidelberg runs a National Clinical Amyloidosis Registry.

Therapy

The different clinical symptoms require patient-specific therapy planning. In most cases, local microlaryngoscopic ablation is sufficient. In some cases, tracheostomy has to be performed to secure the airways [251].

Prognosis

Despite sufficient local therapy, the recurrence rate is approximately 50 %. Systemic therapeutics are useless in cases of localized laryngeal manifestations [248]. Patients who are not appropriate for surgery may undergo radiotherapy. However, data regarding this issue are sparse [252]. Systemic secondary amyloidosis has a poor prognosis; due to the multiple organ affection (especially heart, kidneys, and brain), the disease is often fatal. In contrast to systemic amyloidosis, local amyloidosis has a significantly better prognosis. At this point, the amyloidosis support group is mentioned that may be contacted via www.amyloidose-selbshilfe.de.

Note: If amyloid deposits are found in the larynx, secondary amyloidosis with poor prognosis must be excluded

6.3 Pemphigus vulgaris

Pemphigus vulgaris (PV) is a rare bullous autoimmune disease of the skin and the mucosa. It is caused by circulating autoantibodies against

cadherins in the desmosomes. In cases of PV, antibodies against desmoglein 3 and desmoglein 1 are found. Desmoglein 3 is expressed particularly strongly in the mucosa [253, 254]. Especially laryngeal involvement may cause life-threatening airway obstruction.

Clinical manifestation

PV can manifest in different regions of the head and neck. Lesions of the oral mucosa in the sense of erosions are described in 75–80 % of the cases. The affection of the larynx may lead to symptoms such as stridor, dyspnea, hoarseness, and hemoptysis.
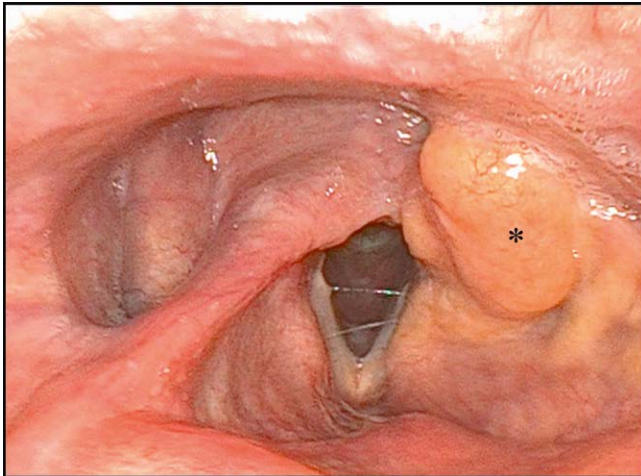
▶ **Fig. 17** Laryngeal amyloidosis. (*) Laryngeal AL amyloidosis of the kappa light chain type left hemilarynx , flexible laryngoscopy (chip/tip).

Diagnosis

ENT examination of the mucosa of the upper aerodigestive tract is essential, skin or mucosal biopsy is mandatory for diagnosis. Histologically, a suprabasal cleft can be confirmed in the HE staining. Additionally, autoantibodies are visualized in the direct immunofluorescence. Antibodies against desmoglein 3 circulating in the blood are confirmed by means of ELISA or indirect immunofluorescence. ELISA is highly sensitive and specific [255].

Therapy and prognosis

Therapy has to be performed interdisciplinarily. This includes the systemic application of glucocorticoids and other immunosuppressants. Rituximab, a monoclonal antibody directed against the B cell antigen CD 20, can also be used for the treatment of PV. Schmidt and colleagues could show that partial remission was achieved in 95 % of the patients [256]. Furthermore, promising innovative therapy concepts are described. They include the so-called chimeric autoantibody receptor (CAAR). The underlying principle is that the disease-causing B cells are recognized by the CAAR and eliminated via T cell activation [257, 258]. If untreated, the disease leads to death. This is caused by dermal fluid loss, superinfections or other complications due to disturbed skin barrier. In cases of adequate therapy, the long-term survival rate is more than 90 %. There is a support group for patients with pemphigus diseases (www.pemphigus-pemphigoid-selbsthilfe.de).

Note: With adequate therapeutic interventions, pemphigus vulgaris of the larynx has a good prognosis.

6.4 Granulomatosis with polyangiitis (GPA)

GPA, formerly called Wegener's granulomatosis, is an idiopathic vasculitis of the middle and small arteries characterized by necro-
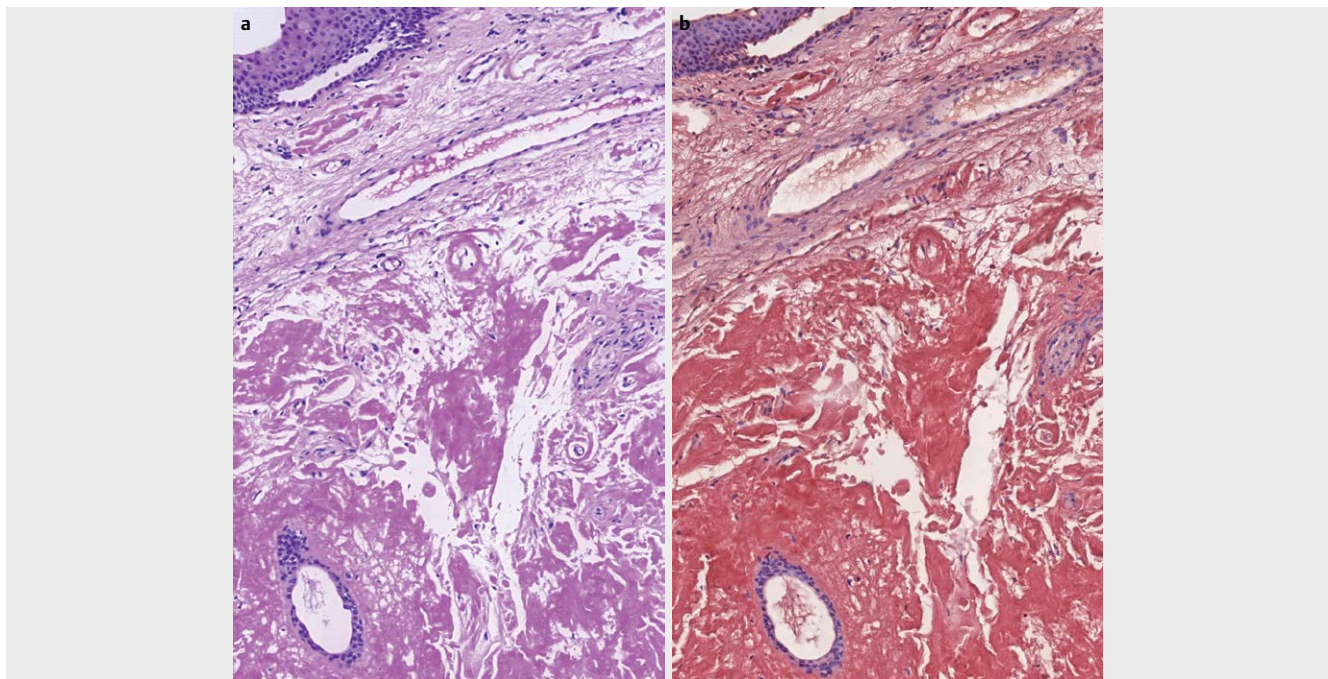
▶ **Fig. 18** Amyloidosis. **a** Laryngeal mucosa with subepithelial, amorphous, extracellular, eosinophilic deposits that in Congo red staining (see **b**) have a characteristic red reaction, corresponding to amyloid.

tizing granulomatous inflammations of the respiratory system as well as a co-existing glomerulonephritis. In Europe, about 10 cases per 1 000 000 people are estimated. GPA is a severe disease; median survival of an untreated generalized form is 5 months, death occurs mainly due to kidney and lung failure. Modern immunosuppressive therapy concepts have significantly improved the patients' prognosis; currently the median survival rate is 21 years after diagnosis [259].

Clinical manifestation

Manifestation in the larynx or trachea in form of ulcers or subglottic stenosis appears irregularly. Rarely, laryngotracheal lesions are the only manifestations of GPA. Subglottic stenosis is found in 10–20 % of GPA patients and often occurs in children. The origin for subglottic stenosis is a destruction of the surrounding tissue due to vasculitis with subsequent reduced blood flow that is associated with excessive fibrosis [260]. Subglottic stenosis with a reduced lumen of up to 70 % usually remain asymptomatic, while severer findings may lead to life-threatening dyspnea, stridor and rarely cough. Up to now, only one case of supraglottic stenosis has been described in the context of GPA [261]. Several pharmaceutics may cause acute episodes, e. g. propylthiouracil, methimazole, carbimazole, sulfasalazine, or minocycline [262].

Diagnosis

The diagnosis of GPA is based on the criteria of the American College of Rheumatology. Two of the following criteria have to be met: involvement of the paranasal sinuses, formation of nodules, mixed pulmonary infiltrates or caverns in the chest X-ray, hematuria or similar changes in the urinary status as well as the histological confirmation of granulomas in the arterial wall or in the perivascular tissue of an artery or arterioles [263]. For clarification, biopsy is required. Serology may differentiate several subtypes of so-called "antineutrophil cytoplasm antibodies" (ANCA), the presence of cANCAs is typical. In acute disease situations, the sensitivity and specificity of the ANCA testing are 91 % and 99 %, respectively. In the context of generalized GPA, the ANCAs are increased in 90–95 % of the cases. In cases of localized organ affection in the head and neck area, the levels are positive only in 50–70 % of the patients [264]. The diagnosis of laryngeal or tracheal manifestation is made primarily by means of flexible endoscopy as well as high-resolution CT of the neck.

Therapy and prognosis

In less advanced cases, pharmacological therapy is sufficient, supported by topical inhalative glucocorticoids or optionally circumscribed surgical procedures may be applied (e. g. laser surgery). The most common pharmacotherapeutic approaches include glucocorticoids as well as cyclophosphamide, rituximab, intravenous immunoglobulins, abatacept, methotrexate, or azathioprine [259]. Despite adequate pharmacotherapy, up to 80 % of the patients need surgical intervention, this includes translesional injection of corticoids, endoscopic dilatations, radial laser incisions, rarely stent applications, tracheostomy, or open resections. As it is well known, each surgical procedure may lead to an increase of the stenosis, so that initial surgical steps should be kept as minimally invasive as possible [265]. Information for affected patients may be retrieved for example via https://gpa-info.org.

Note: Beside cartilaginous damage of the nasal skeleton, subglottic stenosis are regularly occurring manifestations of GPA in the head and neck area.

6.5 Sarcoidosis

In Germany, sarcoidosis occurs with a prevalence of about 50 per 100 000 inhabitants and manifests mainly in the lung and the lymph nodes. An affection of the larynx or trachea is rather rare. An exclusive affection of the head and neck may occasionally be observed [266].
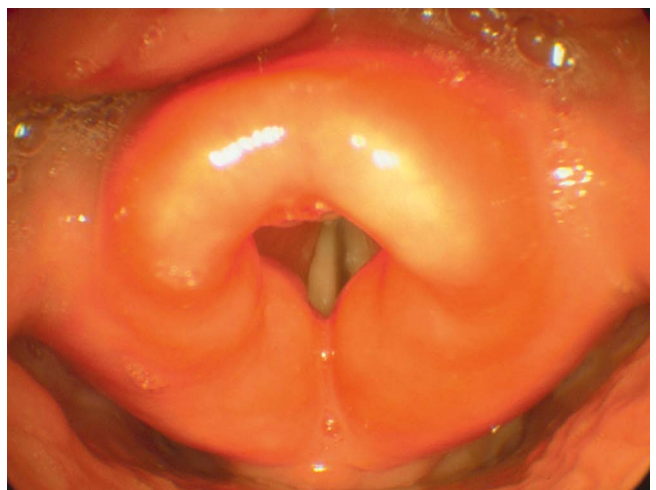
Clinical manifestation

Most patients acquire the disease in the 3rd and 4th decade of life. In rare cases, also children may be affected. Depending on the location, laryngeal sarcoidosis is characterized by dysphagia, dysphonia, cough, or airway obstruction with dyspnea. In cases of mediastinal lymph node sarcoidosis, also recurrent laryngeal nerve paralysis may be observed [267]. A suddenly occurring edematous swelling of the laryngeal tissue is typical, which may cause pseudotumor-like changes. Sometimes, granulomas or ulcerations are also found. The epiglottis and the aryepiglottic folds are affected most frequently with up to 80 % of the cases (▶ **Fig. 19**), although al other laryngeal areas may be affected as well [235, 268].

Diagnostics

The three-pillar model for diagnosis are: the clinical and radiological presentation, the histological confirmation of non-caseating granulomas, and the exclusion of relevant differential diagnoses. For radiological clarification of sarcoidosis a CT of the thorax is required. In acute sarcoidosis, serology shows an increased blood sedimentation rate with normal CRP and frequently an increased overall IgG, serum calcium, and calcium in the urine. The most important differential diagnosis is tuberculosis [269].

Therapy

In cases of acute airway obstruction, appropriate airway protection may be required, in extreme situations tracheostomy is necessary.

▶ **Fig. 19** Laryngeal sarcoidosis. Manifestation of sarcoidosis at the larynx with typical deformity of the epiglottis.

Usually, the course of sarcoidosis is favorable, in more than 50 % of the cases, spontaneous remissions occur after 1–2 years. After 5 years, most cases are spontaneously healed. Hence, therapy completely depends on the severity of the clinical findings. In cases of critical organ affection, corticosteroids are effective, they may even be applied topically. If the larynx is affected, corticosteroids should be applied early to avoid critical airway obstruction. Beside steroids, mitomycin applications are possible as well [270]. In Germany, some self-help groups exist for sarcoidosis patients, e. g. Deutsche Sarkoidose-Vereinigung e. V. and Sarkoidose-Netzwerk e. V.

Note: In most cases, sarcoidosis heals spontaneously. The treatment is performed based on the symptoms.

6.6 Relapsing polychondritis

In the literature, about 100 publications are found on the topic of relapsing polychondritis of the larynx and/or trachea. Mostly, small patient series are presented.

Clinical manifestation

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by recurrent inflammation of hyaline cartilage. The disease has an incidence of 3–4.5:1,000,000, while females are five times more frequently affected than males [271, 272]. The incidence of RP increases with age and has its peak in the 4th decade of life while 5 % of the cases also occur in childhood [273]. The disease is characterized by recurrent inflammation and cartilage destruction, in particular of the ears, nose, and airways [274, 275]. The mechanisms of initiation of RP, maintenance of the pathological immune response, and subsequent cartilage destruction remain largely unclear. Several factors seem to be involved, including genetical conspicuities (HLA-DR4), specific antibodies against cartilage structures (type II collagen, matrilin-1), and the modification of the cytokine and chemokine signatures (MCP-1, MIP-1β, and IL-8) [276–280]. Matrilin-1 is an extracellular matrix protein that is predominantly expressed in the tracheal cartilage [281]. In about 30 % of the cases, additional autoimmune rheumatologic and hematologic pathologies pathologies are observed [274, 282]. Clinically, the duration and severity of the disease may vary significantly. Several organs may be affected, in 50 % of the RP patients, the larynx and the trachea are involved, which can lead to life-threatening laryngotracheal stenosis [283]. A recent study could show that RP is associated with other autoimmune diseases in more than 20 % such as Sjögren's syndrome, autoimmune thyroiditis, systemic lupus erythematosus, antiphospholipid syndrome, or rheumatoid arthritis [284].

Diagnostics

In 1976, McAdam and colleagues established the first criteria of RP [274]. The diagnosis can be made if three of six of the following criteria are met: 1) bilateral auricular chondritis; 2) non-erosive seronegative inflammatory arthritis; 3) nasal chondritis; 4) ophthalmological inflammations; 5) chondritis of the airways; 6) vestibulocochlear disorders [285]. These criteria have been modified by Damiani and Levine and by Michet and colleagues [286, 287].

Therapy

RP patients with mild symptoms are usually treated with nonsteroidal anti-inflammatory drugs (NSAR) and, if necessary, predniso-

lone. In cases of severe manifestations with damage of the airways, higher doses of prednisolone may be required [288]. If steroid resistance develops during treatment, immunosuppressive drugs such as azathioprine, cyclosporine A, and plasmapheresis may be applied [289]. Furthermore, methotrexate is an effective and rather well tolerated drug [290]. Dapsone is an antirheumatic agent with antibiotic effect that may be applied as second-line therapy. However, the manifold side effects have to be taken into consideration. There are some reports about successful therapy with infliximab [291, 292].

Prognosis

The course of the disease is hardly predictable. Recurrent inflammatory reactions of the cartilage lead to permanent destruction of the affected tissue. If this destruction affects the trachea and larynx, serious respiratory problems may occur that can be lethal.

Note: RP is diagnosed based on a symptom score. The disease is treated primarily with medications.

7 Rare diseases of the thyroid

The last chapter will discuss rare diseases of the thyroid. Hereby, the selection was made consciously.

7.1 Riedel's thyroiditis

Riedel's thyroiditis is reported in about 100 publications in the literature. These are nearly exclusively single case reports.

Clinical manifestation

Riedel's thyroiditis is a fibrous thyroiditis. With an incidence of 1 per 100 000 population, it is a rare disease.. The origin of the disease is unknown. There are hints for an autoimmune genesis, however, fibrosing IgG 4 associated disease is discussed as well [293]. A indurated and enlarged thyroid is a typical appearance. In cases of affection of the surrounding structures of the neck, frequently obstruction of the upper airways is observed. Furthermore, dysphagia, stridor and partly even recurrent laryngeal nerve paresis are found.

Diagnostics

The examination reveals a very solid mass in the jugulum that is not displaced relative to the thyroid gland. Usually, a hypothyreodism is seen in the blood tests. Regarding differential diagnosis, a carcinoma may be suspected [294], however, the clinical appearance is still typical. Ultrasound shows a hypoechogenic thyroid fibrosis that is sparsely supplied with blood. CT is helpful to assess an extrathyroidal extension and in estimating the extent of fibrosis [295]. Finally, the diagnosis can only be made by means of open biopsy. Typically, the fibrous tissue is infiltrated by eosinophils. Due to the rarity of the disease, the diagnosis is often delayed. The four diagnostic criteria include 1) extrathyroidal extension of the inflammatory process; 2) presence of occlusive phlebitis; 3) exclusion of granulomas, giant cells, lymphoid follicles, and 4) exclusion of malignancy [296].

Therapy

The treatment comprises the application of glucocorticoids or tamoxifen. Surgical measures are challenging because the thyroid is

difficult to separate from the surrounding healthy tissue. Thus, a circumscribed surgical therapy should only be performed to avoid obstructive symptoms.

Prognosis

The disease has a good prognosis; main cause of death is severe tracheal compression. The mortality rate is 5 % [293].

Note: Riedel's thyroiditis is treated with glucocorticoids, surgical therapy is performed symptom-based, often in the sense of partial resections.

7.2 Allan-Herndon-Dudley syndrome (MCT8 deficiency)

Up to now, 120 articles have been published on the very rare MCT8 deficiency syndrome.

Clinical manifestation

Thyroid hormones are essential for the development and function of the central nerve system. They are transported into the interior of the cells via transmembraneous cellular carrier proteins. One of them is the monocarboxylate transporter 8 (MCT8). MCT8 is specific for the transportation of thyroid hormones and is coded by the SLC16A2 gene. Gene mutation leads to a rare (1-year incidence of 0.1 per 100 000 people) X-chromosomal disease that is known as Allan-Herndon-Dudley syndrome and concerns almost allways men. It is not a thyroid disease in the proper sense,but it is often assigttned to this group. Phenotypically, the patients have severe neurological symptoms such as paraparesis with hypotonia, bradykinesia, spasticity, moderate to severe mental retardation with missing speech development as well as epilepsy [297].

Diagnostics

Typical laboratory constellations include an increased triiodothyronine (T3) plasma level (peripheral hyperthyroidism), reduced thyroxin (T4), and a normal or slightly increased TSH level [297, 298]. Genetic examination is required for clear diagnosis.

Therapy

T3 analogues that do not need MCT8 to pass through the cell membrane could be used as therapeutic agents. They comprise e. g. the T3 analogue of 3.5- diiodothyreopropionic acid and 3,5,3'- triiodothyroacetic acid [299–302]. Another therapeutic option is the application of pharmacological chaperons that allow a conformation stabilization of mutated proteins. In two studies, Braun and colleagues could show that the application of pharmacological chaperons restore MCT8 in the cell membranes and mediate the T3 transport in certain types of SLC16A2 mutations [303, 304].

Note: MCT8 deficiency manifests mainly in form of severe neurological disorders.

7.3 Primary congenital hypothyroidism (CH)

There is a comprehensive data situation of more than 8,000 articles.

Clinical manifestation

Congenital hyperthyroidism (CH) is classified into primary and secondary types. The origins of primary CH are developmental disorders of the thyroid or a deficient thyroid hormone synthesis. Secondary CH is cause by disorders of the central regulation in the hypothalamus or the pituitary gland. The prevalence of the disease varies regionally, which is probably due to the different occurrences of iodine. Generally, primary CH is found in 1:4,000 newborns [305–307].

Diagnostics

The diagnosis is made in the context of the mandatory laboratory testing of newborn examinations (at the U2 examination, 3rd to 10th day of life). The disease is characterized by a reduction or even complete missing of the thyroid hormones T3 and T4 as well as an increase of the TSH level. If during the diagnostic procedure low TSH levels are measured in addition to T3 and T4, the rare form of central hypothyroidism may be assumed that appears with an incidence of 1:20 000 newborns [308].

Therapy

The therapy of choice is the early application of the thyroid hormone of L-thyroxine.

Note: The primary congenital hypothyroidism is diagnosed in the context of obligatory examinations of newborns.

7.4 Medullary thyroid carcinoma

A comprehensive data situation of 8,200 publications is available.

Clinical manifestation

The medullary thyroid carcinoma (MTC) develops from the parafollicular cells of the thyroid that secrete calcitonin. It accounts for approximately 5 to 10 % of all thyroid carcinomas and has an incidence of 0.11 per 100 000 people [309, 310]. The disease occurs sporadically in 75 % of the cases and in 25 % as part of the autosomal dominantly inherited disorder MEN (multiple endocrine neoplasm) type 2 and type 3. MEN type 2 and type 3 are mainly caused by the germ line mutation in the RET proto-oncogene, which encodes a tyrosine kinase receptor [311, 312]. Because of the autosomal dominant inheritance, relatives of MEN patients should undergo human genetic consultation. However, it must be taken into account that a negative family history does not exclude a genetic disposition, as generations may be skipped or new mutations may occur [313, 314]. Furthermore, MTC appears clearly earlier in these patients than in sporadic cases [315].

Diagnostics

The cytological examination by means of fine needle aspiration (FNA) is helpful for the diagnosis of MTC, but it has a variable accuracy. This circumstance is due to the heterogenic cytological appearance of MTC, which may falsely mimic diseases such as follicular neoplasms or sarcomas [309]. Confirmation of MTC is the immunohistological evidence of calcitonin. Serum calcitonin further serves as sensitive peripheral tumor marker. The calcitonin screening is a highly sensitive test for the early detection of MTC [316]. Calcitonin concentrations of 60–100 pg/ml can be a strong indicator for MTC [314]. In cases of slightly increased basal calcitonin, a stimulation test with pentagastrin or calcium is recommended in order to precise the indication for surgery. In case of threshold values of more than 100 pg/ml for stimulated calcitonin, there is an indication for thyroidectomy [314]. Furthermore, mutation analy-

ses are obligatory for all patients with newly diagnosed MTC [309]. MCT do not exhibit iodine metabolism and are therefore not amenable to radioiodine therapy. Another hallmark is the ability to rapidly metastasize to hematogenous and lymphogenous sites. Therefore, early detection is prognostically crucial. , In patients with family MTC, diagnostics of the adrenal medulla and parathyroids are obligatory. Ganglioneuromas on the tongue also allow the assumption of MEN type 2b [317].

Therapy

Total thyroidectomy is the therapy of choice. The indication is made after histological or biochemical diagnosis confirmation of MTC. In cases of stimulated calcitonin levels greater than 100 pg/ml, the indication of surgery is made, whether or not a tumor could detected on imaging. The indication for central and lateral neck dissection is made generously in sporadic MTC. In hereditary types, the decision for prophylactic neck dissection is made depending on the basal calcitonin level. If distant metastases are found, tyrosine kinase inhibitors such as cabozantinib and vandetanib may prolong the progression-free survival with palliative intention [318–322]. Adjuvant radiotherapy should be taken into account in patients with an increased risk of local recurrence or airway obstruction [323]. Prophylactic thyroidectomy in children in cases of confirmed RET mutation is recommended. In high-risk patients, it should be performed already in the first months of life and in risk patients (e. g. mutations in the codon 634) before the age of 5 years [309]. Calcitonin and CEA (carcino-embryonic antigen) are applied for postoperative follow-up of patients with MTC. Of course, beside MTC also accompanying diseases that are associated with MEN, e. g. pheochromocytoma, hyperparathyroidism or other manifestations, have to be treated interdisciplinarily.

Note: MTC is a complex endocrinological disease. It must always be treated interdisciplinarily.

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Conflict of interest

The authors declare that they have no conflict of interest.

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