Orphan Tracheopathies

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Introduction

Within the scope of respiratory medicine, central airway diseases have overall received less attention than parenchymal disorders. This is perhaps based on the incorrect assumption that disease processes involving the trachea and main bronchi are relatively rare and often clinically inconsequential. It may also be based on the unfounded belief that severe cases may only be successfully managed by complex and invasive surgical interventions often associated with high surgical risks. Tracheal diseases encompass a variety of disease processes that may be primary or secondary to underlying systemic diseases, whether inflammatory, infectious, or neoplastic in nature. Central airway diseases can generally be successfully managed by a variety of endoscopic procedures, which, within this past decade, have grown exponentially in both number and complexity. In that regard, central airway diseases present unique challenges and opportunities for respiratory physicians and can be largely credited for the development of the subspecialty of interventional pulmonary medicine.

Anatomical Considerations

The trachea extends from the lower border of the larynx (at the inferior edge of the cricoid cartilage) to the carina where it separates into right and left main stem bronchi. The angle between the right and left main stem bronchi is approximately 70°, with the right main stem bronchus being slightly more vertical than the left. The trachea is lined by a series of 18–22 semicircular cartilaginous rings located anteriorly and laterally, which are responsible for its relatively rigid structure. Conversely, the posterior (membranous) trachea consists of a relatively thin muscular layer made of longitudinally arranged smooth muscle fibers and a fibrous connective tissue forming the "trachealis."

The trachea is an irregular tube that is mostly intrathoracic (lower two-thirds). The average tracheal length is 10 cm in women and 12 cm in men (range, 8–13 cm) [1, 2]. The normal tracheal diameter in men is 13–25 mm coronal and 13–27 mm sagittal, with an average diameter of 19.5 mm [1–3]. In women, the respective values are 10–21 mm coronal and 10–23 mm sagittal, with an average diameter of 17.5 mm [1–3]. Pathological alteration in the size of the trachea refers to tracheal dimensions greater or less than these normal range values.

Clinical Presentation

Although stridor or a central "monophonic" wheeze can occasionally suggest the diagnosis of a tracheal disease, these symptoms are often reported late in the course of the disease and are preceded by less specific symptoms of dyspnea on exertion, cough, and, sometimes, hemoptysis. Tracheal diseases are unfortunately not always evident on plain chest radiography, and, as such, a clinical suspicion should lead to additional investigations.

Significant advances in imaging technologies have transformed our diagnostic approach to central airway lesions. Standard and dynamic computed tomography

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(CT) of the chest including two- and three-dimensional reformatting of images can now identify most tracheopathies and often suggest a precise diagnosis. In addition, chest CTs offer detailed information on the structures surrounding the airways, allowing the distinction between extrinsic compression from extraluminal processes versus endotracheal disease. Pulmonary function studies, particularly when they include a flow–volume curve, are equally invaluable. Fiberoptic bronchoscopy remains the gold standard for the diagnosis of the vast majority of tracheal diseases.

Etiological Considerations

Diseases involving the trachea often lead to debilitating symptoms for patients, and the diagnosis of central airway involvement is often delayed by erroneous diagnoses of more common respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

Diseases of the trachea have been classified by several parameters including luminal narrowing versus widening, focal versus diffuse, congenital versus acquired disorders, and combinations thereof [1, 2, 4, 5]. In addition, tracheal diseases may be classified by an underlying cause. What is considered optimal classification depends on the type of tracheal disease being discussed and the purpose.

The majority of disorders involving the trachea are neoplastic or infectious in nature. However, there are several uncommon tracheal disorders that are of an unknown cause but are associated with characteristic features. Malignancy may occur in the trachea directly by endoluminal involvement, such as squamous cell carcinomas, adenoid cystic carcinomas, or metastases, or indirectly by extrinsic compression from tumors arising from the surrounding structures (e.g., esophageal carcinomas, thyroid carcinomas) or malignant lymphadenopathy. Similarly, traumatic injuries to the trachea from prolonged intubation or previous tracheostomy may ultimately result in significant narrowing or excessive compliance of the trachea, resulting in airflow limitation, or in post-tracheostomy fistula, resulting in massive tracheal bleeding. Other uncommon tracheal diseases are occasionally encountered and often present complex challenges to clinicians due to the lack of evidenced-based guidelines regarding diagnosis and optimal management. These include idiopathic subglottic stenosis, tracheobronchopathia osteochondroplastica, idiopathic tracheomalacia, tracheobronchomegaly, and tracheal involvement in systemic diseases (including granulomatosis with polyangiitis, relapsing polychondritis, sarcoidosis, and tracheal amyloidosis). These so-called "orphan diseases" constitute the topic of this chapter and will be reviewed here, with a particular emphasis on practical management.

Idiopathic Subglottic Stenosis

Clinical Vignette

A 45-year-old Caucasian woman presents to the pulmonary clinic for shortness of breath that has been slowly progressing over the past 2 years. She was diagnosed with asthma several months ago and prescribed various inhalers (bronchodilators and inhaled steroids) but showed no significant improvement. She is otherwise healthy and is not taking any other medications. She had several endotracheal intubations for minor surgical procedures in the past but never remained intubated for prolonged periods of time. She reports occasional heartburn and indigestion that has not been severe enough for her to seek medical attention. Chest radiography is obtained and interpreted as normal. Pulmonary function studies reveal the presence of a moderate airflow obstruction with a normal diffusing capacity. Both inspiratory and expiratory portions of the flow–volume curve are flattened, raising concerns for the possibility of fixed central airway obstruction. A fiberoptic bronchoscopy is performed and reveals a 70% concentric narrowing in the subglottic area without evidence of inflammation or neoplastic infiltration. Biopsies are consistent with nonspecific inflammation, without evidence of granulomas or malignancy. A diagnosis of idiopathic subglottic stenosis is established.

Introduction

Tracheal stenosis may be encountered in a variety of different clinical situations. Tracheal traumas, whether related to prolonged intubation with excessive endotracheal tube cuff pressure, tracheostomy, infections (such as tuberculosis or rhinosclerosis associated with *Klebsiella rhinoscleromatis*), or post-transplant (heart–lung transplant, in which the anastomosis is tracheal rather than bronchial), are causes of secondary tracheal stenosis. Rarely does tracheal stenosis occur as a complication of tracheal malignancy, radiation therapy, inhalational injury, or even congenital causes (such as airway hypoplasia, complete tracheal rings, or extrinsic compression from vascular rings) [6–9]. In a minority of cases, no obvious cause can be identified, and the diagnosis of idiopathic subglottic stenosis (ISS) is established. Of course, the diagnosis is one of exclusion and requires careful exclusion of all other potential causes.

Etiology and Pathogenesis

The first case of ISS was described in 1972 by Brandenburg [10]. Relatively few and small case series have been pub-

lished since, and, overall, our understanding of the underpinnings of this rare entity remains limited.

The vast majority of affected individuals are women, which has led to theories on the role played by the hormonal environment [10–13]. In that context, several investigators have assessed for the presence of overexpressed estrogen and progesterone receptors on the cellular membranes of epithelial and fibroblastic cells involved in the disease process with overall unconvincing results [14, 15].

Although a hormonal basis for the disease remains unsubstantiated at this time, the evident gender predilection remains to be explained otherwise. One hypothesis suggests that other initiating factors may contribute to the disease process, perhaps facilitated by a specific hormonal milieu. Others have postulated that repeated cough trauma, with "telescoping" of the first tracheal ring into the cricoid cartilage, may be followed by an abnormal wound repair process, perhaps driven by specific hormonal influences, though this remains purely speculative [11]. The possibility of the limited form of granulomatosis with polyangiitis (GPA) is always difficult to confidently exclude, as the presentation is by definition limited to the upper airway and the specific serum antibodies may be lacking in up to 40% of the cases of GPA. In addition, biopsies of the upper airway will frequently miss the typical granulomatous changes associated with the disease. Clearly, limited GPA is unlikely to be responsible for more than a small minority of these cases as it would not account for the female predominance observed. Smoking does not appear to play a role.

More convincing arguments have been advanced for the role played by gastroesophageal reflux disease (GERD). Multiple observational studies have reported a higher frequency of GERD in this patient population compared to that in the general population [9, 16–18]. Furthermore, treatment with anti-reflux agents has been associated with improvement in the severity of lesions observed and symptoms experienced by patients. More recently, an elegant case–control study has lent support to this hypothesis by showing increased levels of pepsin, a gastric enzyme generally absent from the upper airway, in tracheal biopsies of patients with ISS [19]. Although causality remains in question, these observations suggest that GERD treatment should be at least considered as part of the management of these patients.

Clinical Features

The most common symptom reported by patients with ISS is exertional dyspnea. Patients generally do not experience dyspnea until the tracheal lumen is severely reduced to less than 10 mm in diameter. Thus, the diagnosis is often delayed as symptoms generally occur late in the course of the disease when a monophonic wheeze or even stridor becomes apparent. Coughing may be present in some patients.

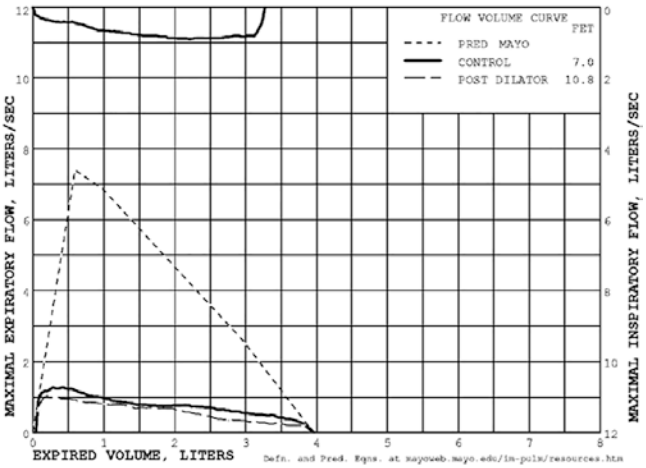

Fig. 5.1 The flow–volume loop in fixed upper airway obstruction (subglottic stenosis) revealing blunting of both the inspiratory and expiratory portions of the loop

Pulmonary Function Studies

Pulmonary function testing in patients with ISS usually demonstrates fixed (versus variable) airflow limitation with a plateau manifesting on both inspiratory and expiratory flow–volume loops (Fig. 5.1) [20, 21]. This is because the airway caliber does not significantly change with variations in intraluminal pressure in most patients with ISS.

Imaging Studies

Conventional chest radiography may reveal narrowing of the tracheal air column but is neither sensitive nor specific to the diagnosis of ISS. A chest CT allows a more precise assessment of the tracheal anatomy and also provides information on the mediastinum, which by definition should appear normal in ISS (i.e., no extrinsic compression). High-resolution CT using multi-row detectors now allows for two- and three-dimensional reconstruction and virtual bronchoscopic images that can help define the type (concentric, complex, hourglass) and extent of stenosis prior to invasive techniques. In addition, dynamic CT with expiratory views allows identification of dynamic collapse due to tracheomalacia occasionally associated with ISS [1, 2].

Bronchoscopy

Bronchoscopy is the gold standard for the diagnosis of tracheal stenosis (Fig. 5.2). Typically, flexible bronchoscopy is used first in order to determine the location, extent, and complexity of the stenosis. Endobronchial ultrasound (EBUS) can document the thickening of the lamina propria of the tracheal mucosa without cartilage involvement. This diagnostic tool can be helpful both in differentiating ISS from other

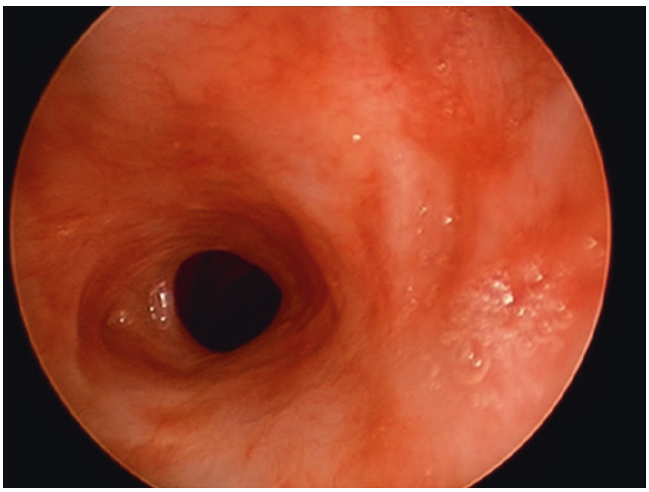

Fig. 5.2 Bronchoscopic view of idiopathic subglottic stenosis in a 38-year-old woman. The tracheal lumen is narrowed to a 4 mm diameter

diseases that usually involve the cartilage (i.e., chondromalacia, relapsing polychondritis) and in assessing the extent and complexity of the tracheal stenosis. Occasionally, the stenosis is severe enough that only pediatric or ultrathin bronchoscopes may be used. In this situation, however, extreme caution is needed as procedure-related edema or inflammation can result in life-threatening airway obstruction. In such cases, proceeding directly to rigid bronchoscopy in a controlled operating room setting may allow better management of the airways. High-frequency ventilation can be used with rigid bronchoscopy and is extremely helpful in this setting.

When obtained, biopsies, by definition, show no evidence of granulomatous inflammation or malignancy. The typical histological finding consists of cheloidal fibrosis with dilatation of the mucous glands and normal cartilage [14]. As mentioned above, studies evaluating the presence of estrogen and progesterone receptors have not been conclusive.

Treatment

The definitive treatment of ISS consists of single-stage laryngotracheal resection with or without a posterior membranous tracheal wall flap. The largest series published by Ashiku et al. from the Massachusetts General Hospital included 73 patients, 67 of whom had excellent long-term results without the need for further endoscopic or surgical interventions with a mean follow-up of 7.9 years [22]. In contrast, the largest case series on endoscopic management of ISS reported recurrence requiring re-intervention in 30% of patients at 6 months and in 87% at 5 years [23]. Although the results would argue for surgical interventions in the majority of patients, it cannot be overemphasized that such patients should be referred to centers of excellence with expertise in the management of this exceedingly rare disease. Cartilage grafting has been used in the surgical management of complex stenotic lesions [24].

Endoscopic treatment varies and is based on expert opinion. It may include simple dilatation using rigid bronchoscopy with barrels of increasing diameter, which may be preceded by radial cuts using laser. Others have used flexible bronchoscopy with balloon dilatation. We tend to favor rigid bronchoscopy, which offers the safety of a more secured airway. Applications of mitomycin C and/or intralesional injections of corticosteroids are sometimes used to prevent recurrences, though the evidence for this practice is scarce. Mitomycin C should not be used during pregnancy. In addition, some reports suggest that the excessive use of mitomycin C may be associated with subsequent tracheal stenosis from excessive fibroproliferation [25]. Airway stents are occasionally considered, but their use may be associated with recurrent tracheal trauma that could jeopardize future definitive surgical treatment. Tracheostomy is believed to present the same risks and is usually discouraged. The value of empiric medical therapy including inhaled steroids and empiric proton pump inhibitors remains unclear at this time, though documented gastroesophageal reflux disease should be aggressively treated.

Idiopathic Subglottic Stenosis: Key Points

- Female predominance
- Location: subglottis
- Histology: cheloidal fibrosis of the lamina propria with preservation of the tracheal cartilage
- By definition of the diagnosis of exclusion, secondary causes of tracheal stenosis should be excluded

Tracheobronchopathia Osteochondroplastica

Clinical Vignette

A 55-year-old man is referred to the urology clinic for prostatectomy after being diagnosed with prostate adenocarcinoma. He is a never smoker but was diagnosed with chronic obstructive pulmonary disease (COPD) a few years back and uses a beta-2 agonist inhaler as needed as well as inhaled steroids. He has moderate obstruction on his pulmonary function test, but his diffusing capacity is normal. He is considered at a low risk for surgery from a respiratory standpoint and undergoes an uneventful radical prostatectomy. After the procedure, the anesthesiologist recommends a pulmonary consultation because of difficulties encountered during endotracheal intubation, requiring placement of a smaller-diameter endotracheal tube. A chest CT scan shows prominent calcified tracheal nodules sparing the posterior membrane with normal lung parenchyma. Fiberoptic bronchoscopy confirms the diagnosis of tracheobronchopathia osteochondroplastica.

Introduction and Clinical Presentation

With less than 400 cases reported in the literature, tracheobronchopathia osteochondroplastica (TPO) is one of the rare tracheal diseases [26]. It is characterized by the nonmalignant growth of cartilaginous and/or osseous submucosal nodules of varying sizes (generally 1–3 mm) that protrude into the lumen of the trachea and proximal main stem bronchi. As they arise from the tracheal cartilages, these nodules typically spare the posterior membrane, which generally helps distinguishing this diagnosis from those of other tracheal diseases. This entity is likely underreported as affected patients are generally asymptomatic or have mild respiratory symptoms.

Etiology and Pathogenesis

TPO affects both males and females with equal frequency and does not appear to be influenced by smoking [27]. Most patients are middle-aged adults, though few cases have been reported in children [26–29].

The pathogenesis of the disease remains obscure, although some have suggested that ongoing irritation from chronic cough may eventually lead to metaplasia of the elastic connective tissue. Biopsies of the lesions of TPO have revealed the presence of bone morphogenetic protein 2 and transforming growth factor beta-1, cytokines involved in extracellular matrix and bone formation [30]. An association with amyloidosis has been described, and some have suggested that TPO could be a manifestation of tracheobronchial amyloidosis, though the evidence supporting this assertion is limited to a few case reports. More likely, these two entities represent distinct tracheal diseases with overlapping clinical manifestations. Finally, *Klebsiella ozaenae*, a bacterium responsible for the development of atrophic rhinitis, has been suggested as a possible cause for TPO as its presence was demonstrated in 20% of TPO patients in a large case series [26–28].

Clinical Features

In the majority of cases, the presence of TPO is incidentally identified on the basis of a chest CT demonstrating calcified submucosal nodular thickening or during bronchoscopy. Occasionally, the confluence of osseous and cartilaginous nodules can lead to mass-like formation, resulting in luminal narrowing and symptomatic tracheal stenosis. Laryngeal involvement may occasionally be seen as well. Hemoptysis, due to ulceration of the mucosa overlying these nodules, is a rare manifestation of the disease and is generally minimal and self-limited. Cough, wheezing or stridor, hoarseness, and recurrent infections (due to poor mucociliary clearance and post-obstructive infections) can occur as well. A characteristic presentation, as described in the case above, is that of difficult endotracheal intubation, eventually leading to the diagnosis.

Pulmonary Function Studies

Pulmonary function studies are frequently normal but may occasionally demonstrate an obstructive defect when the degree of tracheal narrowing causes significant airflow limitation. The central airway location of the disease can be identified by a flow–volume loop showing the plateau of the inspiratory or expiratory portion of the curve depending on whether the level of obstruction is extra- versus intrathoracic, respectively. In some cases (extensive disease or fixed obstruction), both the inspiratory and the expiratory portions may be abnormal [27].

Imaging Studies

Chest radiography is rarely sensitive enough to suggest the diagnosis but may occasionally show narrowing and irregularity of the tracheal air column with calcified deposits. A chest CT reveals the characteristic calcified nodules arising from the anterior and lateral walls of the trachea with varying degrees of narrowing and irregular lumen (Fig. 5.3) [27, 28, 31]. As mentioned earlier, the posterior membrane is typically spared and, if involved, should suggest the possibility of alternative diagnoses, specifically amyloidosis and relapsing polychondritis, which can both result in significant central airway calcifications.

Bronchoscopy

Bronchoscopy typically establishes the diagnosis and reveals obvious abnormalities in the vast majority of patients, which may range from mild to severe. Submucosal nodules protruding into the airway can be seen at all levels of the trachea (Fig. 5.4) but result in clinically significant narrowing

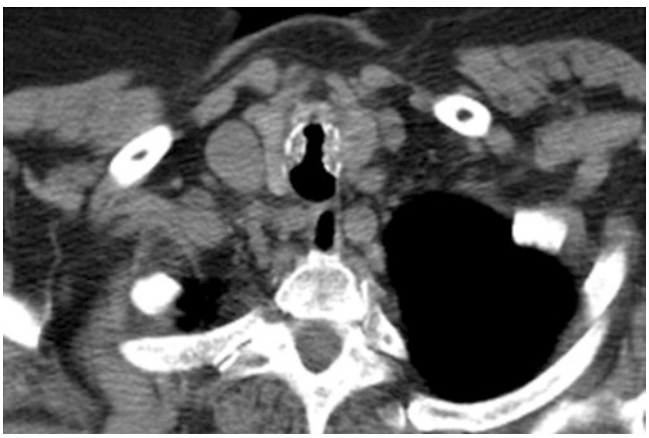

Fig. 5.3 A CT scan of the chest of an 89-year-old woman with tracheobronchopathia osteochondroplastica. Partially calcified submucosal nodules are present in the tracheal walls with sparing of the posterior membranous wall

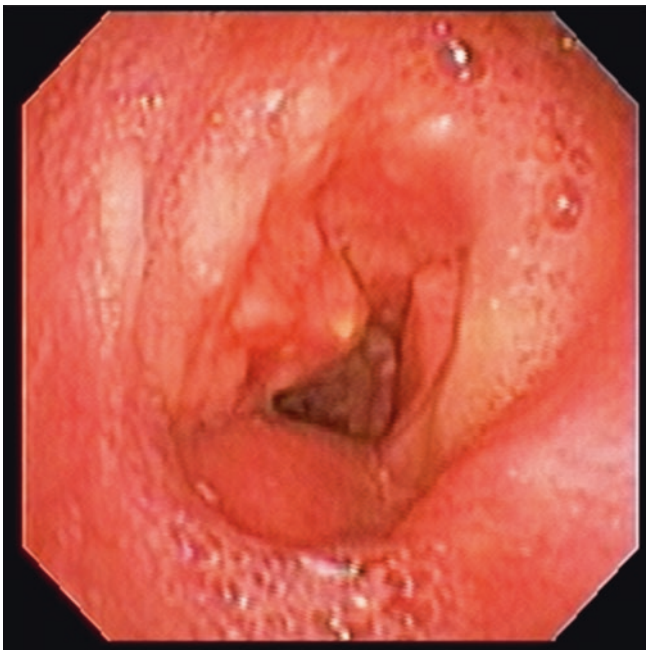

Fig. 5.4 Bronchoscopic view of tracheobronchopathia osteochondroplastica revealing osseous submucosal nodules projecting into the tracheal lumen

(>50%) in only a minority of patients. While the posterior membrane is generally spared, progression of the nodule formation may eventually extend posteriorly in 15% of patients. Biopsies are not mandatory to establish the diagnosis when palpation with forceps confirms the firmness of the calcified and/or osseous nodules. When biopsies are obtained, which can be difficult, they reveal the presence of submucosal cartilage and bone formation with occasional intraosseous bone marrow formation. Proximal main stem bronchi may be involved as well, but more distal airways are involved in less than 20% of patients [27, 29].

Treatment

In the absence of respiratory symptoms, patients with TPO do not require any specific treatment. In symptomatic patients, treatment of TPO remains mainly supportive. Bronchopulmonary hygiene measures aimed at improving secretion clearance are of paramount importance in patients with recurrent infections due to impaired mucociliary function and post-obstructive infections. Immunizations should be updated. The definitive treatment of TPO is difficult, as the firm, calcified, and osseous nodules do not lend themselves well to endoscopic resection. Furthermore, the diffuse extent of the lesions along the tracheal walls often precludes any consideration of reconstructive surgery. When indicated, rigid bronchoscopy with resection of the nodules using gentle and careful pressure with the bevel of the bronchoscope is usually the most efficient but may result in tracheal injury. Other techniques have been described, including laser-assisted mechanical debulking. An important caveat is that any consideration of endoscopic treatment should be symptom-driven, as the lesions of TPO are minimally progressive in most patients and follow a benign course [27, 29, 32].

TPO: Key Points

- No gender predilection
- Tracheal involvement typically spares the posterior membrane
- Biopsies are not needed in typical cases
- Differential diagnosis on CT imaging includes amyloidosis and relapsing polychondritis

Tracheomalacia

Clinical Vignette

A 55-year-old man with known COPD is admitted to the pulmonary ward for his third episode of pneumonia this year. His cough has worsened with production of purulent sputum and increased shortness of breath. Chest radiography reveals consolidation in the right lower lobe. Pulmonary function studies reveal severe obstruction, markedly worse than that noted 2 years prior to admission during an outpatient evaluation. A chest CT scan confirms the right lower lobe infiltrate but is otherwise unremarkable. A bronchoscopy is undertaken to explore the possibility of an endobronchial lesion. The bronchoscopy reveals severe tracheobronchomalacia from excessive dynamic airway collapse secondary to severe laxity of the posterior membrane. The pulmonary service is consulted for management recommendations.

Introduction

Tracheomalacia (from the Greek word *malakia*, i.e., softness) refers to a weakness of the trachea that results in increased compliance and excessive reduction in the tracheal luminal dimensions during normal or forced expiration and/or inspiration. Because the trachea is mainly intrathoracic (lower two-thirds approximately), most of the changes noted occur during expiration, as the airways tethered to the surrounding thoracic structures remain relatively normal during inspiration [33, 34]. The extrathoracic portion of the trachea is occasionally involved as well, and

inspiratory collapse with audible stridor may then occur. When the proximal bronchi are involved, the appropriate term is "tracheobronchomalacia." The distinction is essentially semantic as the manifestations and clinical implications are identical.

Tracheomalacia may be diffuse, as seen in excessive dynamic airway collapse, or focal, as seen in complications of tracheostomy, for example. In general, focal lesions are more easily amenable to endoscopic or surgical treatment, emphasizing the importance of a careful endoscopic examination. It has been argued that tracheomalacia should only refer to excessive tracheal weakness from structural insufficiency of the tracheal cartilaginous rings and should be distinguished from excessive dynamic airway collapse, related to excessive laxity of the posterior membrane. As these conditions may result in similar manifestations and management strategies, this distinction is not particularly helpful and, rather, management should be guided by symptoms and evidence of airflow limitations during dynamic respiratory maneuvers.

Etiology and Pathogenesis

The vast majority of cases described in children is congenital and include mucopolysaccharidoses (such as Hurler syndrome and Hunter syndrome) and Williams–Campbell syndrome (the absence of cartilages, resulting in loss of structural support) [1, 35, 36]. Other causes of tracheomalacia in children include compression of the trachea by vascular rings or the right-sided aortic arch. The persistent compression of the trachea is believed to result in chronic ischemic changes and cartilage destruction, eventually leading to focal tracheomalacia. Bronchiectasis is likely to develop over time as a consequence of recurrent lung infections from retained secretions, and, as such, tracheomalacia should be considered in the differential diagnosis of diffuse bronchiectasis.

Various types of tracheomalacia are described in adults. As for children, prolonged tracheal compression from surrounding structures may eventually result in focal tracheomalacia. This includes chronic endotracheal intubation with excessive cuff pressure, tracheostomy or other forms or trauma to the airways, extrinsic compression from tumoral processes or lymph nodes, and thyroid goiters. Other causes include infections (such as tuberculosis) or, rarely, heart–lung transplant (as the anastomosis is located in the lower trachea). Some inflammatory conditions may result in diffuse tracheomalacia, such as relapsing polychondritis (discussed separately) and inhalational injuries (including recurrent aspirations). Tracheomalacia from excessive dynamic airway collapse is typically observed in COPD, though occasionally occurring in never smokers. In this condition, documentation of central airflow limitation should precede therapeutic interventions as excessive dynamic airway collapse may be secondary to peripheral airflow limitation and may not contribute to the patient's respiratory symptoms [37].

Idiopathic tracheomalacia is relatively rare. One type of idiopathic tracheomalacia is Mounier-Kuhn syndrome, or tracheobronchomegaly, which typically manifests in adult life (also discussed separately) [33–35, 38–42]. Another example is Williams–Campbell syndrome, which is a congenital disorder characterized by the absence or severely diminished cartilages in the tracheobronchial tree (mainly affecting the fourth- through sixth-order bronchi) and results in bronchiectasis and, in some patients, tracheomalacia [38, 39, 41]. This condition is usually diagnosed in children or young adults.

There are few descriptions of the histopathological changes associated with tracheomalacia. Autopsy studies have revealed atrophy of the longitudinal muscle fibers with or without cartilaginous destruction or absence of the cartilaginous support structure [33, 34]. Inflammatory cellular infiltrates may also be noted in some instances, such as in relapsing polychondritis [43].

Clinical Features

Clinical manifestations are nonspecific and vary based on the degree of luminal narrowing, often resulting in delayed diagnosis or misdiagnosis as having chronic bronchitis or refractory asthma [33, 34]. Some asymptomatic patients may decompensate only during episodes of respiratory infections or during sleep (due to sleep-related respiratory changes and recumbent position). Symptomatic patients may experience wheezing, typically described as monophonic and, rarely, stridor when the extrathoracic portion of the trachea is involved.

Recurrent infections are secondary to impaired mucous clearance and are a common presentation. They may eventually lead to the development of bronchiectasis, aggravating the obstructive syndrome and predisposing patients to yet further infections. Cough may be severe and occasionally result in cough-induced syncope.

Pulmonary Function Studies

Pulmonary function studies usually reveal airflow obstruction. The severity of this obstruction is directly proportional to the degree of tracheomalacia [33, 34]. Obstruction that is considered out-of-proportion to the smoking history of a COPD patient should suggest tracheomalacia from excessive dynamic airway collapse. One clue to the diagnosis is the presence of a plateau on the expiratory portion of the flow–volume curve, following a reduced peak expiratory flow rate.

Oscillations of flow, similar to those noted in obstructive sleep apnea patients, have been reported as well. If the extrathoracic portion of the trachea is involved, then a plateau may also be noted on the inspiratory curve [33, 34, 44]. In some instances, a cardiopulmonary exercise test with flow–volume loops may help to document central airflow limitation as exercise-limiting.

Imaging Studies

Chest radiography is usually inadequate for the diagnosis of tracheomalacia. Chest CT images may also be misleading if obtained only during inspiration, as the tracheal dimensions are generally normal under these conditions (unless the extrathoracic trachea is involved as well). If a diagnosis of tracheomalacia is suspected, then a dynamic CT study should be obtained by requesting dynamic expiratory imaging. The diagnostic accuracy of dynamic CT approaches that of bronchoscopy and allows precise measurements of the luminal diameter changes and extent of tracheomalacia [1, 2]. Multirow detector spiral CT allows for image acquisition within seconds and is generally obtainable even in the most dyspneic patients. The type of luminal narrowing can be accurately characterized by CT. Reduction in the anteroposterior diameter is described as crescent-shaped (a "frown sign" on CT images) (Fig. 5.5), whereas reduction in the sagittal diameter has been referred to as "saber-sheath trachea." This latter presentation is more common in patients with emphysema and is believed to result from chronic cough with microfractures of the cartilages and lateral compression from hyperinflated upper lobes.

The criteria for tracheomalacia on CT are identical to those used during bronchoscopy. By convention, airway collapse is considered significant if the minimum luminal diameter is 50% or less than the maximum diameter. Luminal narrowing down to 25% is considered moderate, and complete collapse is designated as severe [33]. These criteria are supportive of the diagnosis but should be considered diagnostic only in the appropriate clinical setting, as several studies have shown that a majority of healthy controls can experience narrowing >50% during forced expiratory maneuvers [45, 46]. For this reason, a 75% narrowing cutoff has been proposed by some authors for diagnosing tracheomalacia [45–47].

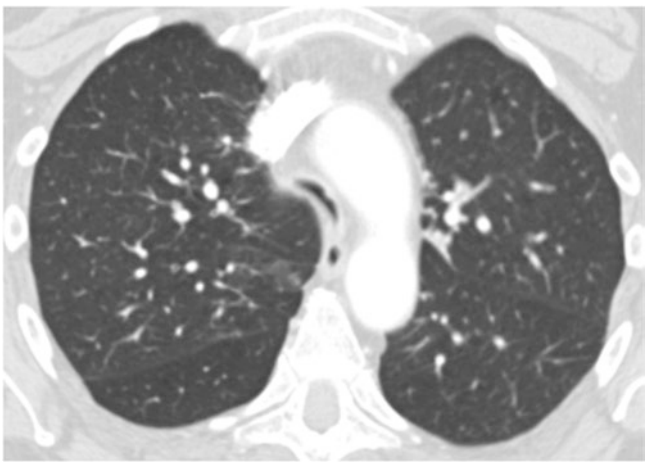

Fig. 5.5 A CT scan of the chest of a 57-year-old man with severe tracheomalacia demonstrating the "frown sign"

Bronchoscopy

Bronchoscopy remains the diagnostic gold standard, although it does not provide the same quantitative measurements of airway diameter assessed by CT imaging. Again, a narrowing >50% is considered consistent with the diagnosis but is based on a semiquantitative assessment by bronchoscopists.

Bronchoscopy should be performed with conscious sedation as it allows maneuvers of cough and forced expiration that are not possible under general anesthesia. Morphometric bronchoscopy has been proposed as a potential tool to allow quantitative analysis of airway dimensions via software analysis of digital bronchoscopic images, but its use remains experimental at the present time. One major advantage of bronchoscopy over CT is the possibility of identifying endoluminal pathology responsible for the tracheal narrowing, which may be missed by CT. In addition, bronchoscopic interventions may be possible in the same setting or allow adequate planning for further interventions.

Treatment

Treatment of tracheomalacia should be individualized according to the type, extent, and etiology of the tracheomalacia. Treatment of the underlying cause, when possible, is warranted (such as systemic anti-inflammatory treatment of relapsing polychondritis or resection of mediastinal mass). If possible, tracheomalacia in children should be observed as it may spontaneously resolve as the patients get older and the cartilaginous support structures mature. Noninvasive measures such as continuous positive airway pressure (CPAP) therapy during sleep have been suggested, particularly in the context of excessive dynamic airway collapse, and may allow improved airflow and decreased compliance, though the supportive evidence overall remains scarce [33, 34, 48].

Focal lesions are sometimes amenable to tracheal resection and end-to-end anastomosis, which is considered the definitive treatment. When the tracheomalacia is diffuse, or when the patient is not deemed an appropriate candidate for surgical treatment, endoscopic interventions may be helpful. Rigid bronchoscopy with silicone stent placement may result in significant improvement in lung function and symptoms.

Migration of the choke point beyond the extremities of the stent may limit its efficacy, however, and excessive stent length can lead to further impairment of mucous clearance and predispose patients to recurrent infections. Inhalation of nebulized saline is warranted after stent placement to avoid inspissation (thickening) of mucous and occlusion of the stent. Metallic stents, while similarly efficacious in re-establishing airway patency, should be avoided in benign airway diseases, as they are associated with serious long-term complications. As opposed to silicone stents, they can be difficult to remove when left in place for prolonged periods of time.

An alternative option for diffuse diseases is surgical tracheobronchoplasty, which consists of reinforcing the posterior membrane of the central airways with prosthetic material such as Marlex mesh, effectively resulting in splinting of the airways [49–51]. Potential candidates for this procedure should be selected on the basis of a favorable response to silicone stenting [33]. Long-term stenting is an option for those who do respond but are not considered acceptable candidates for this invasive procedure. Airway stabilization via tracheoplasty or stenting for COPD-associated excessive dynamic airway collapse can result in significant improvement in quality of life and physiological parameters [52]. In some cases, tracheostomy may occasionally be performed if the area of narrowing can be successfully bypassed.

Tracheomalacia: Key Points

- Increased compliance of the trachea with collapsibility
- May be idiopathic or secondary
- May be focal or diffuse
- Effects of endotracheal stent placement can predict response to surgical management

Tracheobronchomegaly

Clinical Vignette

A 30-year-old man with a history of recurrent respiratory infections and refractory asthma presents to the emergency department for a sudden onset of shortness of breath. Chest radiography reveals a right-sided pneumothorax, and chest tube thoracostomy is performed for management. A chest CT is obtained to assess for the underlying parenchymal lung disease, which reveals significant bronchiectasis that predominates in the lower lobes with marked enlargement of the central airways. A bronchoscopy later confirms the diagnosis of tracheobronchomegaly. Several tracheal diverticula are noted during the bronchoscopic examination.

Introduction

Idiopathic tracheobronchomegaly, also called Mounier-Kuhn syndrome, was first reported in an adult patient in 1932. Since then, more than 100 cases have been reported in the literature [33]. It is considered a congenital disease affecting the trachea and proximal bronchi, resulting in abnormal enlargement of the airways, leading to tracheobronchomalacia with impaired secretion clearance and recurrent infections. Although occasionally identified during childhood, the disease more often presents later in life after development of bronchiectasis and recurrent infections prompt further investigations.

Etiology and Pathogenesis

Abnormal enlargement of the central airways has been described in association with a variety of conditions including connective tissue diseases such as Marfan syndrome, Ehlers–Danlos syndrome, and ankylosing spondylitis [53–59]. Congenital diseases have also been reported in association with tracheobronchomegaly and include Bruton agammaglobulinemia, Kenny–Caffey syndrome, ataxia telangiectasia, and Brachman de Lange syndrome. Finally, similar to traction bronchiectasis, fibrotic infiltrative lung processes have occasionally been reported to cause enlargement of the central airways tethered to the surrounding fibrotic lung parenchyma. These conditions include idiopathic pulmonary fibrosis and other chronic parenchymal lung diseases such as sarcoidosis, rheumatoid-associated interstitial lung disease, chronic histoplasmosis, and idiopathic pleuroparenchymal fibroelastosis [60, 61]. The term "Mounier-Kuhn syndrome" should be reserved for the idiopathic form of the disease and is also called idiopathic giant trachea. Several familial cases have been described [62].

Clinical Features

Mounier-Kuhn syndrome tends to affect males with a higher frequency [4, 56, 63, 64]. Although the anatomical anomalies are generally present in childhood, the symptoms usually become evident in adulthood, in the 30s or 40s. A significant percentage of patients with Mounier-Kuhn syndrome are asymptomatic and are diagnosed on the basis of abnormalities identified on imaging studies (typically chest CT) obtained for other reasons. Associated symptoms mainly consist of chronic cough and shortness of breath, recurrent infections, increased sputum production, and bronchiectasis. Occasionally, patients may report episodes of hemoptysis. Rare cases of pneumothorax have been reported [65].

Pathophysiology

The pathophysiology of Mounier-Kuhn syndrome remains to be elucidated. Histopathology data are limited but suggest that the tracheal and bronchial walls contain an abnormal connective tissue responsible for weakness of the central airways, leading to significant tracheobronchomalacia. Atrophy of the smooth muscles and elastic component of the airway walls has been described in autopsy studies [66–68]. The resultant tracheobronchomalacia causes reduction of airflow, impaired secretion clearance, and recurrent infections, ultimately leading to bronchiectasis. Outpouchings of the tracheal mucosa, or airway diverticula, may develop over time, and are highly suggestive of the diagnosis when identified by chest CT imaging. These may result in additional secretion retention, potentially further increasing the risk of infectious complications.

Pulmonary Function Studies

Pulmonary function studies are typically consistent with an obstructive pattern. As described in other types of tracheomalacia, an expiratory plateau may be identified, suggesting central airway obstruction. Restrictive defects are rare but may occasionally be seen when pulmonary fibrosis is present.

Imaging Studies

Chest radiography may occasionally suggest the diagnosis, which is confirmed by the presence of central airway enlargement on chest CT (Fig. 5.6). The diagnosis is established when the airway diameter exceeds the following cutoffs, which represent three standard deviations above the norm: 24 mm for the right main stem bronchus, 23 mm for the left main stem bronchus, and 30 mm for the trachea [1, 3].

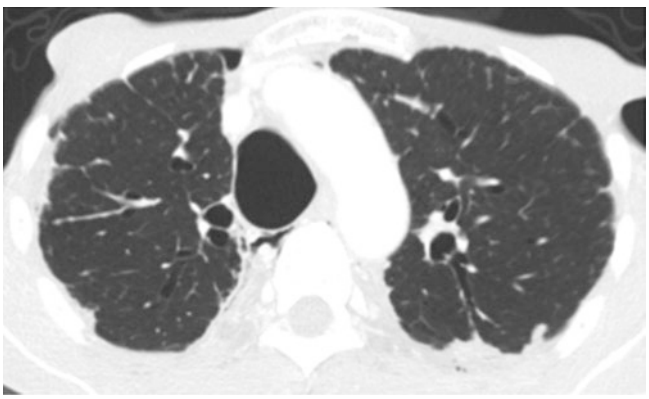

Fig. 5.6 A CT scan of the chest of a 66-year-old man with tracheobronchomegaly. The anteroposterior diameter is 37 mm

Treatment

Treatment of Mounier-Kuhn syndrome is challenging. The size of the central airways often precludes endoscopic stenting due to the lack of appropriately sized stents. The largest stent deployed in a case of tracheomegaly in association with Marfan syndrome had an outer diameter of 2.8 cm and had to be custom-made [69]. Despite this, a recent case series has reported improvements in quality-of-life indices and physiological parameters after both endoscopic stenting and surgical tracheobronchoplasty in patients with Mounier-Kuhn syndrome [70]. One anecdotal report described lasting improvement with low-power yttrium aluminum perovskite laser treatment of the posterior membrane of a Mounier-Kuhn patient, causing effective retraction of the tissues, though the safety of this approach remains questionable [71].

Supportive interventions such as noninvasive positive pressure ventilation at night, bronchopulmonary hygiene measures, and appropriate and timely antibiotic treatments and immunizations are recommended. The prognosis of the disease varies widely, but severe cases can progress to respiratory failure [4, 56, 63, 64]. Few patients with Mounier-Kuhn syndrome have undergone lung transplantation, and, as for cases of severe bronchiectasis, a bilateral lung transplant is preferred over a single lung transplant [72].

Tracheobronchomegaly: Key Points

- Male predominance
- Diagnosis is typically made in early adulthood
- Recurrent infections and bronchiectasis are common
- Endoscopic treatment is difficult due to the large size of the affected airways

Tracheopathies Associated with Systemic Diseases

The trachea and proximal main bronchi are sometimes involved in a variety of systemic diseases occasionally discovered during the workup of respiratory symptoms. Consideration of these diseases in patients with central airway disorders is warranted as they may influence management and prognosis. As a comprehensive review of all clinical entities potentially associated with central airway involvement is clearly beyond the scope of this chapter, we will review herein the most common offenders: relapsing polychondritis, granulomatosis with polyangiitis, sarcoidosis, and amyloidosis.

Relapsing Polychondritis

Clinical Vignette

A 42-year-old woman presents with shortness of breath and stridor. She has a past medical history significant for hearing loss of unclear etiology and mitral regurgitation. Physical examination reveals a saddle nose deformity and central wheezing on lung auscultation. Chest radiography reveals no apparent abnormalities. Blood work reveals increased inflammatory markers with elevated sedimentation rate and C-reactive protein. A chest CT suggests tracheal narrowing, and a bronchoscopy is performed. Endoscopic examination reveals subglottic stenosis, marked inflammation throughout the tracheobronchial tree, and severe tracheobronchomalacia. Upon further questioning, the patient reports recurrent episodes of ear inflammation and a diagnosis of relapsing polychondritis is established.

Introduction

Relapsing polychondritis is a rare type of autoimmune connective tissue disease that affects both males and females with equal frequency [73]. It is characterized by recurrent episodes of inflammation involving various cartilaginous structures including the ears, nose, upper airway (including the larynx), joints, and cardiac valves (mitral and/or aortic valve regurgitation). In addition, the disease may also result in life-threatening complications affecting the kidneys and central nervous system (CNS). It is most commonly diagnosed in middle-aged adults [43, 73–75].

Unilateral or bilateral ear inflammation is the most common presenting symptom and ultimately occurs in the vast majority of patients during the course of the disease [73, 76]. Approximately 30% of patients will report hearing loss or dizziness related to vestibular involvement. This constellation of symptoms in patients with central airway involvement should suggest the diagnosis of relapsing polychondritis. The characteristic auricular chondritis seen in the majority of patients with relapsing polychondritis is not a feature of granulomatosis with polyangiitis. However, differentiating relapsing polychondritis from granulomatosis with polyangiitis can sometimes be difficult because both diseases can manifest saddle nose deformity and tracheobronchial involvement; the possible overlap between these two entities has been discussed earlier. A biopsy of the tracheal cartilage shows degeneration with fibrous changes and inflammatory cell infiltration. The histological picture is not absolutely characteristic, and specific diagnostic tests are lacking.

Clinical Features

Central airway involvement is common in patients with relapsing polychondritis [77]. The largest case series reported by Ernst et al. [78] included 145 patients, 31 of whom had evidence of airway involvement (21%) with a majority being female (70%). The respiratory manifestations consisted of subglottic stenosis in eight patients (26%), focal or diffuse tracheobronchomalacia in 15 patients (48%), and focal stenosis in the remainder [78]. Other reports suggest that central airway manifestations may occur over time in approximately half of patients with relapsing polychondritis [74, 78, 79]. Presenting manifestations are nonspecific and include chronic cough, wheezing and/or stridor, and hoarseness in case of laryngeal involvement [74, 79].

Laboratory Findings

Laboratory abnormalities are also generally nonspecific, and the diagnosis remains essentially clinical. Anemia of chronic disease may be present, and eosinophilia is noted in approximately 10% of patients. Inflammatory markers are elevated during periods of active disease but may be normal between exacerbations. They are helpful for monitoring the disease and for treatment decisions but do not exclude the diagnosis when normal. Autoantibodies are sometimes present, consisting of antinuclear antibodies in approximately half of the patients. Rheumatoid factor and antiphospholipid antibodies are occasionally noted. Anti-neutrophil cytoplasmic antibodies (ANCAs) have also been described in relapsing polychondritis. Since patients with active limited granulomatosis with polyangiitis have a 30% chance to be ANCA-negative, this laboratory test does not always allow a clear distinction between relapsing polychondritis and granulomatosis with polyangiitis.

There is strong support for an autoimmune process directed at some extracellular components of the cartilage, but no particular antibody has been identified as either sensitive or specific to the disease. Anti-type II collagen antibodies, in particular, are found in a variety of other conditions and are believed to result from a nonspecific immune reaction to cartilage destruction, rather than being true pathogenic antibodies. The utility of identifying these antibodies in clinical practice is unclear [80, 81].

Pulmonary Function and Imaging Studies

Pulmonary function studies reveal findings consistent with central airway obstruction that may predominate during expiration in case of tracheobronchomalacia or may be present during both inspiration and expiration with a fixed stenosis pattern on the flow–volume curve if subglottic stenosis is present. Chest radiography is generally not helpful in the diagnosis. A chest CT reveals

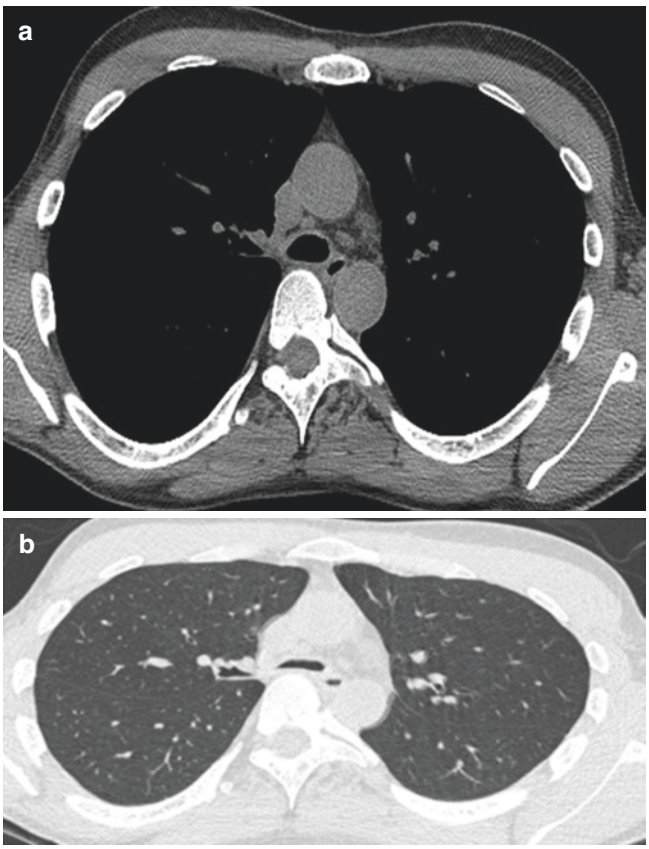

Fig. 5.7 A CT scan of the chest of a 32-year-old man with relapsing polychondritis. (**a**) Inspiratory view demonstrating a thickened tracheal wall with mild narrowing. (**b**) On expiration, there is collapse of the tracheal lumen

changes consistent with tracheobronchomalacia on dynamic images (Fig. 5.7a, b) or subglottic stenosis. One clue for the diagnosis of relapsing polychondritis is the presence of extensive calcification of the walls of the trachea and main bronchi, also seen in a few other conditions (age-related changes, tracheobronchial amyloidosis, and tracheobronchopathia osteochondroplastica). In a retrospective study of 18 patients with relapsing polychondritis referred to chest CT with expiratory images, abnormalities were noted in the majority of patients and consisted of malacia in 13 patients, air trapping in 17, and calcification of the airway wall in seven [82].

Magnetic resonance imaging has been proposed as a way to distinguish inflammation from fibrosis of the soft tissues of the central airways, but problems with resolution and prolonged image acquisition time in patients with respiratory compromise limit its usefulness in clinical practice [83]. Positron emission tomography using ^{18}F-fluorodeoxyglucose has also been suggested to assess for ongoing inflammation, but its use remains largely experimental [84–86].

Treatment

Treatment of the underlying disease using anti-inflammatory and immunomodulating agents is warranted during periods of active inflammation. First-line agents include dapsone or glucocorticoids. Severe life-threatening manifestations of the disease (including cardiac and central nervous system disease) should be treated with high-dose glucocorticoids, often combined with cyclophosphamide or other immunomodulatory agents such as azathioprine, cyclosporine, and methotrexate. Biologics, including tumor necrosis factor inhibitors, have been reported to be effective in some patients [77, 87]. In general, the evidence supporting their use is comprised of observational data and anecdotal reports. Supportive measures should include prophylaxis for *Pneumocystis jirovecii* while on immunosuppressive therapy, prompt initiation of antibiotics when needed, and appropriate immunizations.

The management of airway manifestations should be individualized. Treatment of subglottic stenosis and tracheobronchomalacia should follow the general guidelines outlined in the previous chapters (see Idiopathic Subglottic Stenosis and Tracheomalacia). Endobronchial ultrasound (EBUS) can be useful in the diagnosis and treatment of relapsing polychondritis. EBUS can reveal changes in the tracheobronchial cartilage characterized by fragmentation and edema. Evaluation of the complexity and extent of the stenosis and of the size of residual tracheal lumen facilitates stent placement. Noninvasive positive pressure ventilation may be of help in patients with significant tracheobronchomalacia. It should be emphasized that endoscopic treatment of airway lesions should preferably be performed during inactive phases of the disease as airway manipulations during exacerbations may result in paradoxical inflammatory reactions, resulting in additional airway compromise. Overall, airway manifestations of relapsing polychondritis can usually be controlled with a combination of anti-inflammatory agents and airway-specific interventions, leading to better outcomes than reported in earlier studies [43, 74, 79].

Relapsing Polychondritis: Key Points

- Inflammation of the cartilages, particularly the ears
- Saddle nose deformity and central airway obstruction may mimic granulomatosis with polyangiitis
- Treatment of the underlying inflammation is warranted, when present

Granulomatosis with Polyangiitis

Clinical Vignette

A 32-year-old woman with a long-standing history of granulomatosis with polyangiitis (initially diagnosed by proteinase 3 (PR3)-ANCA positivity and nasal biopsy) is admitted to the pulmonary ward for worsening shortness of breath. She has been treated with various immunosuppressive agents over the years and most recently has been started on rituximab for worsening renal function and several episodes of pulmonary capillaritis with alveolar hemorrhage. Although these manifestations have been well-controlled, she now presents with significant dyspnea on exertion with obvious stridor on deep inspiration. A chest CT excludes obvious pulmonary embolism or parenchymal infiltrates. A bronchoscopy reveals severe subglottic stenosis without evidence of inflammation or other tracheobronchial lesions.

Introduction

Granulomatosis with polyangiitis is an autoimmune multisystem disease characterized by necrotizing granulomatous inflammation involving small-to-medium-sized blood vessels and capillaries. The disease is characterized by the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCAs) with cytoplasmic staining (c-ANCA) directed against the PR3 antigen. PR3-ANCAs are present in 90% of patients with active disease [88].

The respiratory system and the kidneys are most commonly affected (pulmonary renal syndrome), but many other organs may be involved as well, including the central or peripheral nervous system, eyes, heart, gastrointestinal system, and skin. A limited form of the disease is characterized by manifestations in the respiratory system (sinuses and lungs) without kidney involvement. c-ANCAs are positive in only 60% of those with the limited form of the disease [2, 89, 90].

Clinical Features

Respiratory manifestations vary and include chronic rhinosinusitis, pulmonary nodules that may cavitate, diffuse alveolar hemorrhage, and tracheobronchial involvement [88]. Thromboembolic disease is also relatively common during the active phase of the disease.

Tracheobronchial involvement occurs in approximately 15–55% of patients and mostly consists of subglottic stenosis [90]. This subglottic stenosis is indistinguishable from the idiopathic form, and, in general, biopsies fail to show typical necrotizing granulomas or vasculitis. Occasionally, palisading granulomas and microabscesses may be identified. Subglottic stenosis may be the only manifestation of limited GPA. Other less common but well-described airway lesions include concentric lower tracheal or bronchial stenosis, synechial bands resulting in obliteration of smaller airways, submucosal tunnels, polypoid mass lesions (inflammatory pseudotumors), and, less commonly, tracheobronchomalacia. Distal airways may be involved as well with follicular bronchiolitis, bronchiectasis, and, rarely, bronchiolitis obliterans [2, 89, 90].

Pulmonary Function Studies

Pulmonary function studies are important in the evaluation and follow-up of patients with GPA. Obstructive pattern is common, and the flow–volume loop may be consistent with intrathoracic obstruction (a plateau on the expiratory portion of the loop) or a combined intra- and extrathoracic (fixed upper airway) obstruction pattern, as in cases of subglottic stenosis (both inspiratory and expiratory plateaus are present).

Imaging Studies

A chest CT is extremely useful in characterizing the type and extent of the airway lesions. Expiratory images may reveal dynamic airway changes not otherwise obvious on conventional inspiratory images. The tracheal wall may be thickened and occasionally calcified. Although bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA, a chest CT allows for precise quantitative analysis of the type and extent of the stenosis and helps plan appropriate endoscopic interventions.

The utility of positron emission tomography in granulomatosis with polyangiitis has been reported in few case reports [91]. We have occasionally used positron emission tomography to document ^{18}F-fluorodeoxyglucose uptake in the subglottic region and to identify other possible localizations of the inflammatory process.

Bronchoscopy

Bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA. It also helps determine the activity of the disease, by showing significant inflammation not evident by other imaging methods. Mucosal erythema, ulcerative lesions, and cobblestoning of the mucosa are common during the active phase of the disease, whereas noninflammatory fibrotic stenoses are seen between exacerbations [89, 90, 92]. EBUS shows circumferential thickening of the submucosa with an intact bronchial cartilage. It is important to avoid aggressive endoscopic airway interventions during exacerbations as procedure-induced inflammatory reactions may result in further complications.

Treatment

Treatment should consist of remission induction regimens if GPA is active, using a combination of corticosteroids and immunosuppressive agents, such as cyclophosphamide or rituximab. Once the inflammation is controlled, bronchoscopic interventions consist of airway dilatation using balloon tracheo- or bronchoplasty, occasionally preceded by radial cuts using laser or electrocautery. The management of subglottic stenosis follows the same general guidelines described in a previous chapter (see Idiopathic Subglottic Stenosis above). Mucosal applications of mitomycin C and submucosal injections of steroids are occasionally performed in the same episode to prevent recurrence, though the evidence supporting this practice is limited [89, 90, 93]. Similarly, inhaled corticosteroids are of unclear benefit in this situation. Stent placement should generally be avoided but is occasionally necessary. Surgery is sometimes an option for patients who fail to respond to the above measures but should also be considered only after remission.

Granulomatosis with Polyangiitis: Key Points

- May be limited (i.e., limited vasculitis), mostly involving the upper airway
- Subglottic stenosis is the most common form of upper airway involvement
- Biopsies are frequently nondiagnostic (consider instead kidney or sinus biopsies)
- Treatment of the underlying inflammation is warranted, when active disease is present

Tracheobronchial Amyloidosis

Clinical Vignette

A 55-year-old man is referred to a tertiary center for management of tracheobronchial amyloidosis. The diagnosis was established after a bronchoscopy was conducted during an episode of pneumonia and revealed subtle infiltration of the tracheal mucosa including the posterior wall; biopsies demonstrated amyloid deposition. Although the patient is now completely asymptomatic, he has read extensively about his condition and inquires about the risk of cardiac complications and the role for external beam radiation as a potential treatment for tracheobronchial amyloidosis.

Introduction

Amyloidosis refers to a broad and heterogeneous group of diseases caused by the abnormal extracellular accumulation of insoluble fibrillar proteins [94]. This accumulation ultimately results in organ dysfunction and related clinical manifestations. Virtually all organs may be involved, though cardiac, renal, and pulmonary manifestations are generally responsible for the most severe manifestations of the disease. More than 30 different serum proteins have been shown to be responsible for amyloidosis, the most common being related to light chains (AL amyloidosis), serum amyloid A protein (AA amyloidosis), and transthyretin (ATTR amyloidosis) [94]. Amyloidosis may be congenital or acquired and may be limited to one organ or may result in multisystem manifestations.

Clinical Features

Pulmonary manifestations of amyloidosis include pulmonary edema associated with amyloid cardiomyopathy, pleural disease, interstitial lung disease with characteristic septal thickening, pulmonary nodules (amyloidomas), pulmonary hypertension, laryngeal amyloidosis, and tracheobronchial amyloidosis [95]. Tracheobronchial amyloidosis is a rare manifestation of the disease overall and is usually present as a form of localized amyloidosis (i.e., limited to the airways) [95, 96]. It is more common in men and becomes apparent in the fifth or sixth decade of life.

Symptoms are nonspecific and may include cough, sputum production, hemoptysis, wheezing, or stridor, depending on the severity of the airway obstruction. Associated laryngeal amyloidosis may result in significant hoarseness. Distal endobronchial involvement may also be present, potentially leading to post-obstructive pneumonia or atelectasis.

Pulmonary Function Studies

Pulmonary function studies reveal findings that generally correlate with the degree of airway involvement and may be normal in mild cases or reveal airflow obstruction in more severe cases. The flow–volume loop may reveal plateauing of the inspiratory and/or expiratory loop, depending on the anatomical level and extent of obstruction (see preceding chapters). Mixed obstructive/restrictive lung disease is possible in cases of combined airway and interstitial lung disease but is uncommon.

Imaging Studies

Chest radiography is generally not helpful in the diagnosis of tracheobronchial amyloidosis. A chest CT may reveal an irregular and thickened tracheal wall with occasional mass-like lesions protruding into the lumen (Fig. 5.8) [96, 97]. One characteristic finding is tracheal and bronchial calcifications,

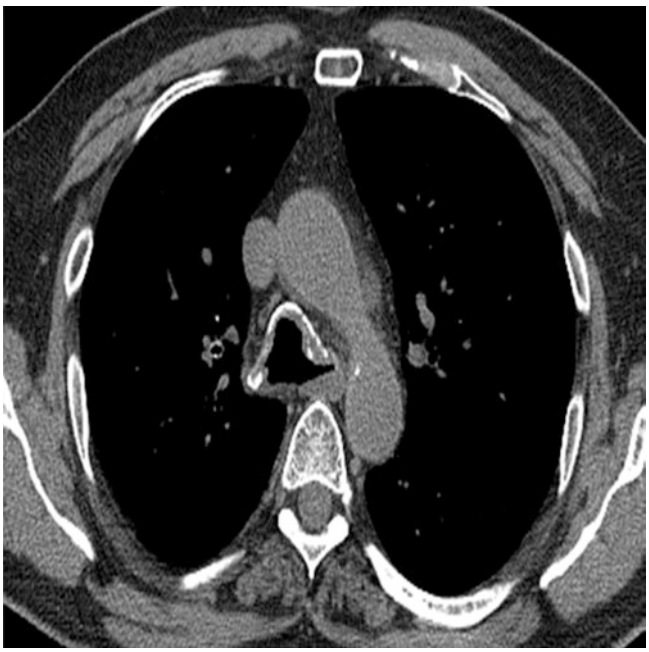

Fig. 5.8 A CT scan of the chest of a 64-year-old man with tracheobronchial amyloidosis demonstrating nodular thickening of the tracheal wall with calcifications

for which a limited differential diagnosis exists (age-related changes, relapsing polychondritis, and tracheobronchopathia osteochondroplastica). The main differential diagnosis is tracheobronchopathia osteochondroplastica, with the notable difference that the posterior membrane is typically uninvolved in tracheobronchopathia osteochondroplastica, though both conditions have been shown to occasionally occur in the same individual. Imaging using positron emission tomography may help distinguish amyloid deposits from malignancy, showing limited ^{18}F-flurodeoxyglucose uptake on delayed images in amyloidosis [98].

Bronchoscopy

Bronchoscopy is warranted to establish the diagnosis. Tracheobronchial amyloidosis is typically characterized by the presence of raised waxy yellowish or erythematosus nodules that may bleed easily on contact or during biopsies. Cobblestoning of the mucosa due to submucosal amyloid deposition may also been seen. Lesions may be focal or diffuse in extent. EBUS shows a thickening of the bronchial mucosa without infiltration of the deeper tissues. EBUS can be helpful in directing the site of biopsy to avoid bleeding, assisting in the choice of the more appropriate endobronchial intervention as reported for other nonmalignant causes of tracheal stenosis (relapsing polychondritis, granulomatosis with polyangiitis, and idiopathic subglottic stenosis). The diagnosis is established on the basis of positive staining with Congo Red, with a typical apple-green birefringence when viewed under polarized light.

Treatment

Treatment for tracheobronchial amyloidosis should be individualized based on the severity of the clinical manifestations and the extent of the disease. Rigid bronchoscopy is often needed in the management of cases of severe endoluminal obstruction using mechanical debulking with or without laser therapy. Endotracheal and/or endobronchial stents are rarely needed unless tracheobronchomalacia is present. Surgery is rarely an option, but tracheostomy may be considered if it can successfully bypass the area of narrowing. As tracheobronchial amyloidosis most often is an organ-limited disease, systemic therapies are generally not needed. Several reports suggest that external beam radiotherapy may be of benefit in patients with symptomatic tracheobronchial disease [99, 100]. As usual, supportive care should include appropriate antibiotics when needed, immunizations, and bronchopulmonary hygiene measures. Prognosis varies widely with some patients remaining stable over many years, whereas others gradually deteriorate with a poor 5-year survival [96].

Tracheobronchial Amyloidosis: Key Points

- Usually limited to the respiratory tract (i.e., no extrapulmonary involvement)
- Congo Red stain of the biopsy specimen demonstrating apple-green birefringence seen under polarized light establishes the diagnosis
- Biopsy may result in significant bleeding
- Treatment is symptomatic and external beam radiation therapy may have a role

Sarcoidosis

Clinical Vignette

A 35-year-old man with a past medical history of stage I sarcoidosis develops hoarseness and shortness of breath. Chest radiography suggests mediastinal lymphadenopathy, unchanged when compared to previous chest radiographs. A chest CT reveals slightly enlarged mediastinal and hilar lymphadenopathy but no obvious infiltrates. Narrowing of the proximal right main stem bronchus is noted, and bronchoscopy is performed. Infiltration of the laryngeal tissue is noted with limitation of the vocal cord movements but no true paralysis. The trachea is diffusely involved with inflammation and cobblestoning with marked narrowing of the origin of the right main stem bronchus. Biopsies confirm the presence of non-necrotizing granulomas without evidence of malignancy.

Introduction

Sarcoidosis is a multisystem disease characterized by the presence of non-necrotizing granulomas in the absence of an identifiable cause. Multiple organs may be affected by the disease, but the predominance of the respiratory manifestations (>90% of the cases) suggests that an inhaled offender may trigger an exuberant type IV immune reaction responsible for the manifestations of the disease. Sarcoidosis can also affect many other organs including the heart, eyes, skin, peripheral and central nervous systems, joints, and kidneys.

Respiratory manifestations of sarcoidosis are varied and include mediastinal and hilar lymphadenopathy, micronodular parenchymal infiltrates, and pulmonary fibrosis. Rare manifestations of the disease include cavitary lesions (as in necrotizing sarcoid granulomatosis), pleural effusions, pulmonary hypertension, and airway involvement including laryngeal and tracheobronchial sarcoidosis [101, 102].

Pulmonary Function Studies

Pulmonary function studies may be normal in mild cases of airway involvement in sarcoidosis or may reveal various combinations of obstructive and/or restrictive defects depending on the extent and severity of intrathoracic involvement. Central airway involvement can result in characteristic abnormalities in the flow–volume curve with an inspiratory and/or expiratory plateau depending on the location and extent of the tracheobronchial lesions.

Imaging Studies

Although bronchoscopy remains the gold standard, imaging studies may offer supportive evidence of the diagnosis. Chest radiography is rarely normal in sarcoidosis and typically reveals mediastinal and/or hilar lymphadenopathy with varying degrees of reticular or reticulonodular infiltrates, but the central airways are difficult to evaluate. A chest CT may show airway distortion or extrinsic compression from adjacent enlarged lymph nodes. Mucosal involvement may manifest as thickening of the wall of the trachea or main stem bronchi. Additional findings suggestive of sarcoidosis include micronodular infiltrates in a perilymphatic distribution and reticular, fibrotic changes that typically predominate in the upper and mid lungs.

Bronchoscopy

Central airways are less commonly involved than distal airways in sarcoidosis. Granulomatous inflammation results in thickening of the tracheal and bronchial mucosa with a characteristic "cobblestone" appearance and may lead to significant obstruction of the airway lumen [102]. Other manifestations include hypervascularity of the mucosa, granular infiltration, plaques, and polypoid lesions. Although symptomatic tracheobronchial sarcoidosis is relatively uncommon, up to 60% of patients with sarcoidosis will exhibit some types of endobronchial abnormalities, making bronchoscopy the diagnostic method of choice when sarcoidosis is suspected [102]. In fact, non-necrotizing granulomas are frequently observed on random endobronchial biopsies in patients with asymptomatic sarcoidosis, particularly when the biopsies are relatively deep and include submucosal lymphatic vessels. Occasionally, the airways may be narrowed as a consequence of extrinsic compression by enlarged mediastinal and hilar lymph nodes. A typical presentation is that of the "right middle lobe syndrome" in which the right middle lobe bronchus is easily compressed by regional lymphadenopathy, leading to impaired secretion clearance and recurrent infections. Finally, severe cases of upper lobe fibrosis may result in airway distortion with resultant fibrostenosis and central airway obstruction [101–103].

Treatment

The treatment is tailored to the severity of the airway involvement. In asymptomatic disease, monitoring without specific treatment is generally appropriate. In advanced disease, systemic corticosteroids may be warranted, whereas mild cases may be treated with only inhaled steroids. Bronchoscopic interventions can include balloon tracheo- and/or bronchoplasty and laser resection with or without stent placement [104–108].

Respiratory Tract Sarcoidosis: Key Points

- Tracheal stenosis is a rare manifestation of sarcoidosis. Biopsies are usually diagnostic, revealing non-necrotizing granulomas
- Treatment with inhaled or systemic steroids may be beneficial

Orphan Tracheopathies: Conclusions

Diseases specifically affecting the trachea are uncommon compared to other respiratory diseases. As such, the diagnosis of tracheopathy is often delayed and affected patients are commonly misdiagnosed to have other conditions such as asthma or COPD. Clues hinting at the possibility of central

airway lesions include stridor or monophonic "central" wheezing and poor response to bronchodilator therapy. Pulmonary function studies can provide important clues, particularly when the shape of the inspiratory/expiratory flow–volume curve is evaluated. Advances in the acquisition protocols of CT imaging and image resolution have considerably improved the identification and characterization of tracheal diseases, but bronchoscopy remains the gold standard in the diagnostic evaluation and can allow assessment for specific interventions. Treatment of the underlying cause is warranted whenever possible. The approach to diagnosis and management should include a multidisciplinary team of clinicians, radiologists, pathologists, and interventional pulmonologists.

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