Chapter 6
Tracheobronchial Amyloidosis

Gustavo Cumbo-Nacheli, Abigail D. Doyle and Thomas R. Gildea

Introduction

Tracheobronchial amyloidosis (TBA) is a disease characterized by extracellular deposition of eosinophilic, proteinaceous, and insoluble β-pleated sheets of fibers within the airways. These insoluble proteins disrupt the airway function. When the pulmonary system is involved in systemic amyloidosis, it may display different features: diffuse interstitial or alveolar septal disease, nodular disease, intra- and extrathoracic adenopathy, pleural disease, and diaphragmatic deposition. In contrast, localized pulmonary involvement manifests as nodular opacities, diffuses opacities, or tracheobronchial disease, the latter being the most common of the three [1].

In this chapter, we review the clinical features of TBA and discuss the role of radiographic imaging, bronchoscopy, and radiation therapy in the management of TBA.

Clinical Features

TBA represents only 0.5 % of all symptomatic tracheobronchial lesions [1]. Symptoms suggesting a form of obstruction, with cough, dyspnea, wheezing, hemoptysis, and hoarseness, are the most common complaints. More than half of the

G. Cumbo-Nacheli
Pulmonary and Critical Care Division, Spectrum Health Medical Group, Grand Rapids, MI, USA

A.D. Doyle (✉)
Department of Internal Medicine, Metro Health Hospital, 5900 Byron Center Avenue, Wyoming, MI, USA
e-mail: abigail.doyle@metrogr.org

T.R. Gildea
Pulmonary, Allergy, Critical Care and Transplant, Cleveland Clinic, Cleveland, OH, USA

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cases may present as obstructive pneumonia, bronchiectasis, or atelectasis [2]. Clinical features are difficult to recognize, often leading to delay in diagnosis and treatment. Routine chest radiography may be unremarkable in up to 70 % of affected patients [1, 3]. TBA tends to be misdiagnosed as asthma, COPD, and pneumonia [3]. CT of the chest often shows soft-tissue thickening and irregular narrowing of the tracheobronchial lumen, which should be further investigated by bronchoscopy [4]. Bronchoscopy with biopsy remains the gold standard for diagnosis. Although TBA nearly always presents in the absence of systemic amyloidosis, the systemic form should be ruled out with serum and urine electrophoresis, electrocardiogram, echocardiogram, and fat pad biopsy. TBA has been reported in association with Sjogren syndrome [5, 6], sarcoidosis [7], and rheumatoid arthritis [8].

Radiographic Appearance

CT findings of TBA can be defined by several characteristics that separate it from other central airways diseases. Typically, there are multiple nodular eccentric lesions in the tracheal lumen. These can occur circumferentially and may contain calcification (Fig. 6.1a–f). The posterior tracheal wall is involved in the disease process. This feature separates it from tracheopathia osteochondroplastica and relapsing polychondritis which spare the posterior wall [9]. There appear to be 2 primary appearances of TBA diffuse airway infiltration and either focal or multifocal nodular infiltration [10]. Some have proposed a "wavy path sign" of nodular appearance along an airway in coronal views [11]. PET-CT with intense uptake of 18-fluorodeoxyglucose by the amyloid material is used to assess activity and can be used as an adjunct to bronchoscopy in follow-up [12].

Bronchoscopy

Bronchoscopy is the primary management tool for TBA from both a diagnostic and a therapeutic standpoint. Endobronchial examination shows either diffuse mucosal infiltrate or nodules (Fig. 6.2). The mucosal lesions have a tendency to have a yellowish hue and bleed easily and ooze considerably longer than typical lesions. Therefore, planning for hemorrhage management should be in place [13, 14]. Other newer imaging techniques have been used. Narrow band imaging (NBI) has been reported to show a complex vasculature and abrupt-ending large caliber vessels [13]. Probe-based confocal light endomicroscopy has also been reported to show "dappled" images of protein deposition [15].

Therapeutic bronchoscopy options include neodymium:yttrium aluminum-garnet (Nd:YAG) laser photo-resection, argon-plasma coagulation, and rigid debulking. When luminal patency is compromised balloon dilation, in some cases airway stenting has been used.

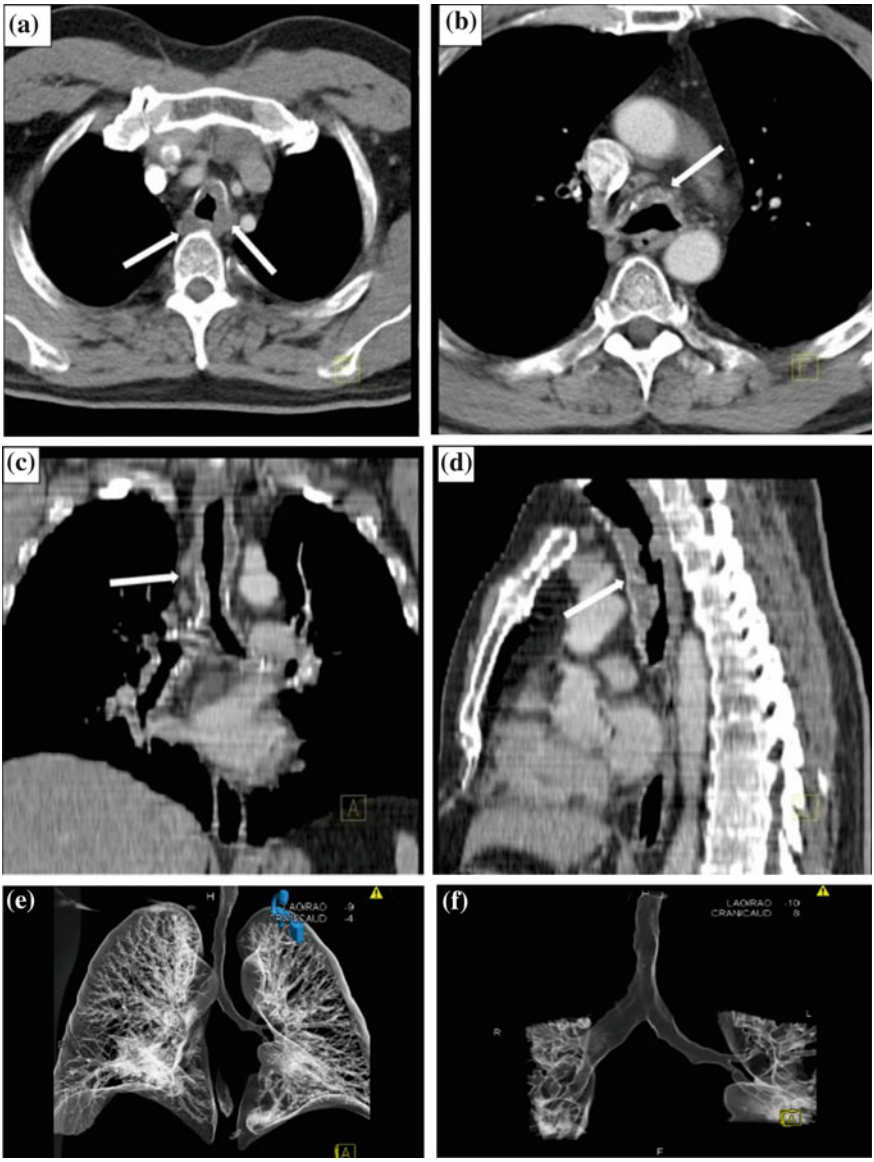

Fig. 6.1 **a** Axial CT image of the trachea demonstrating eccentric nodular masses along the posterolateral wall (*closed white arrow*). **b** Axial image from the same patient at the level of the carina and main-stem bronchi demonstrating diffuse circumferential wall thickening with foci of calcifications and luminal narrowing (*closed white arrow*). **c**, **d** Sagittal and coronal contrast-enhanced CT showing diffuse circumferential thickening of the tracheobronchial airway. **e**, **f** 3D external rendering showing airway narrowing, irregular tracheobronchial mucosa. Note right middle lobe subsegmental collapse. Distal airways are patent

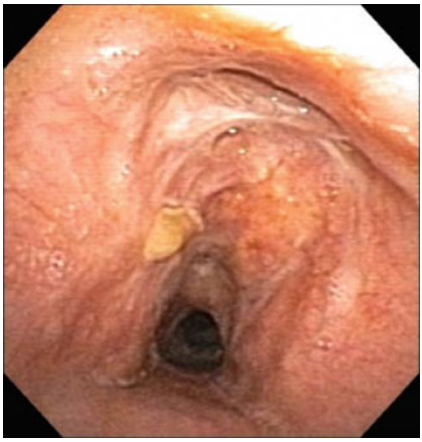

Fig. 6.2 Bronchoscopic findings in a case of tracheobronchial amyloidosis

Fiorelli et al. [16] described a clinical case of a 67-year-old woman diagnosed with TBA, who underwent rigid bronchoscopy with the removal of the mass by mechanical resection and Nd:YAG laser coagulation, followed by placement of a self-expanding, covered Y-stent. Her respiratory symptoms improved immediately, and at five-month follow-up, the CT and bronchoscopic examination showed normal patency of the tracheobronchial tree without recurrence of amyloid deposition. Resection alone may not prevent recurrences, as they often recur within 12 months after resection. A retrospective study performed by Alloubi et al. [17] investigated the long-term outcome of six patients with primary TBA. All patients underwent rigid bronchoscopy and received laser therapy by Nd:YAG prior to mechanical debulking, with the hypothesis the laser therapy would decrease intrabronchial bleeding. A satisfactory tracheal size and resolution of symptoms were obtained after 3–5 sessions of rigid bronchoscopy in 4 of 6 patients, and the other two patients received a silicone stent due to extreme stenosis or re-stenosis of the trachea by tumor-like tissue without improvement after repeated bronchoscopy. All patients had immediate symptomatic improvement, and there were no intraoperative or perioperative deaths. Brill et al. [18] described a case of TBA successfully treated with argon-plasma laser treatment, which achieved recanalization of the bronchus, resulting in sustained clinical improvement.

Medical Therapy

There are few reports of effective therapy for TBA. Systemic pharmacotherapy with colchicine, melphalan, dimethyl sulfoxide (DMSO), and glucocorticoids has been reported with modest success [2, 17]. Toxic side effects from systemic chemotherapy render this therapeutic approach less preferable [1]. Mucolytics, antibiotics,

nebulizer treatments, and occasional courses of oral or inhaled corticosteroids may be used as adjunctive therapy in addition to bronchoscopic debulking [1].

Radiation Therapy

Low-dose external beam radiation therapy (EBRT) has been demonstrated to be effective as an adjunct to bronchoscopic management. In contrast to mechanical debulking and laser therapy, which yields immediate symptomatic improvement, EBRT has a more gradual onset of action. Advantages of EBRT include less bleeding than with bronchoscopic intervention, and higher accessibility to lesions that may not be amenable to bronchoscopic intervention. The mechanism of radiation for control of pulmonary amyloidosis is not completely understood. Some hypotheses provide improvement in localized amyloidosis due to the anti-inflammatory effects seen in early radiation, along with inhibition of localized plasma cells, as chronic inflammation is one of the important factors which stimulates amyloid formation [19]. Others hypothesize the mechanism of action could include a radiation effect on the vasculature, or the induction of immune responses against the deposits by causing local inflammation [10]. Side effects have been reportedly low, with esophagitis the main adverse event [19].

Combination therapies appear to be the most successful form of treatment for TBA patients. In a case report by Kurrus et al. [20], a multimodal approach to treatment with TBA was discussed. The patient underwent EBRT, with a dose of 20 Gy, to the distal tracheal and right main-stem bronchus. Repeat bronchoscopy showed the treated tissue to be less thickened and friable; however, there were new areas of occlusion by amyloid tumor in the right upper lobe, which was resected using a Nd:YAG laser and forceps. The bronchus intermedius was dilated and a silicone stent was placed. The right lower lobe eventually became obstructed; in contrast, the areas that had received the EBRT 7 months earlier continued to appear less thickened, red, and friable. Due to these results, they elected to treat the distal disease progression with the same dose of EBRT as used previously. Patient free of symptoms, with bronchoscopic examination essentially unchanged.

Ren and Ren 12 used EBRT with 24 Gy in 12 fractions, 5 fractions a week over 18 days on two patients diagnosed with TBA [19]. On day two, case one noticed significant improvement in dyspnea, and CT chest showed obvious abatement of the irregular thickness of the bronchial wall, and improvement of PFTs was from moderate obstruction to normal. Follow-up bronchoscopies showed abatement of the lesions, smoother mucosa, and less obstruction, and she remained symptom-free at follow-up of 54 months. Case two also noted symptomatic improvement by day two, with improvement in PFTs two months later, and stable improvement at 46 months follow-up.

A retrospective review of 10 patients with biopsy-proven airway amyloidosis (3 laryngeal and 7 TBA) who underwent EBRT at a median dose of 20 Gy showed local control in 8/10 patients at a median 6.7 years of follow-up. This was defined

by CT and endoscopic evaluation showing no changes in airway wall thickening, decreased mucosal edema, and stable endobronchial pathologic findings, along with improvement in FEV1 [21]. Monroe et al. [22] described a case of extensive TBA involving the right main-stem bronchus and extending inferiorly into the right lower lobe, making surgical debulking and laser therapy difficult. The patient underwent treatment with EBRT at 24 Gy, resulting in significant improvement in respiratory status, imaging, and PFTs within 2 months. At one year, repetitive bronchoscopy showed airways to be patent. Among a cohort of 7 TBA patients with TBA treated by EBRT, all subjects displayed symptom improvement after receiving EBRT. This treatment modality was well tolerated, with the most common side effect being acute esophagitis [23].

Conclusion: Being aware of TBA in the differential diagnosis of many pulmonary symptoms and being familiar with unusual disease imaging is helpful and a key to pattern recognition for expert clinicians. There is no gold standard treatment for TBA, and management is targeted at maintaining airway patency. Treatment modalities include mechanical debulking, balloon dilation and stenting, APC, laser therapy, EBRT, and cryotherapy. The advantages of rigid bronchoscopy over flexible bronchoscopy include airway safety, ability to perform mechanical debulking, and the ease of blood and airway secretion removal [17] but add the risk of airway trauma and inciting bleeding. Being aware of the possible diagnosis and having the ability to obtain diagnostic tissue and perhaps perform simple endobronchial therapeutic procedures to improve airway lumen in a single procedure favored as an initial step but further medical evaluation, management, and consultation with radiation oncology complete comprehensive management.

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