Atul C. Mehta a  Khawaja Salman Zaki a  Amit Banga a  Jarmanjeet Singh a  Thomas R. Gildea a  Valeria Arrossi b

a Respiratory Institute and b Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio, USA

Tracheobronchial Smooth Muscle Atrophy and Separation

Introduction

The tracheobronchial tree plays an indispensable role in airway dynamics. Bronchoscopic advancements have broadened our knowledge and granted us the ability to discover rarities in the tracheobronchial tree. Tracheobronchial smooth muscle or pars membranacea atrophy

Key Words

Airway smooth muscle atrophy · Chronic obstructive pulmonary disease · Tracheomalacia · Tracheobronchomalacia · Excessive dynamic airway collapse · Inhaled corticosteroids

Established Facts

• Tracheobronchomalacia and excessive dynamic collapse of the central airways are being diagnosed with increasing frequency.
• Inhaled corticosteroids are commonly used in patients with obstructive lung disease.

Novel Insights

• Progression of excessive dynamic collapse could result in the rupture of the tracheobronchial smooth muscle.
• Inhaled corticosteroids may play a role in causing atrophy and rupture of the tracheobronchial smooth muscle.

Abstract

We report a case series involving 4 patients with chronic obstructive pulmonary disease who were on an appropriate medical regimen including a high dose of inhaled corticosteroids (ICS). During bronchoscopy, patients were found to have an excessive dynamic collapse of the posterior wall and its separation from the ends of the adjacent cartilaginous rings. This was causing a near-total occlusion of the tracheal and bronchial lumen during exhalation, thereby presenting with an obstructive pattern on the pulmonary functions. We suspect that this was caused by the atrophy of the smooth muscles of the tracheobronchial wall. We reviewed the literature to explore the mechanisms causing atrophy of the bronchial smooth muscle, focusing on the potential role of long-term ICS use.

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and its separation from the cartilaginous rings (tracheobronchial smooth muscle atrophy and separation, TB-SMAS) are one such bronchoscopic finding which, to our knowledge, has not been reported in the literature. This atrophy and separation could be related to a number of etiologies including smoking, chronic inflammation, infection, or drugs like steroids and beta-agonists used in the management of chronic obstructive pulmonary disease (COPD) and bronchial asthma.

Herein, we present 4 cases of TB-SMAS with a literature review on the subject. We hypothesize on the potential role of long-term use of inhaled corticosteroids (ICS) in causing airway smooth muscle (ASM) atrophy and propose mechanisms that could explain their contribution in causing TB-SMAS.

Case Report

Case 1
A 72-year-old female with a history of recurrent sinopulmonary infections, gastroesophageal reflux disease, erosive arthritis, and bronchiectasis was referred for further evaluation and management of an airway abnormality. The latter was first observed during bronchoscopy in the year 2000 by her referring physician who was concerned about the bronchomalacia. The patient first experienced symptoms in the year 2000, and 4 years later, she underwent a sinus drainage procedure and turbinectomy. She continued to have postnasal drip, chronic productive cough, and ear infections requiring the placement of tympanostomy tubes. Her multiple pulmonary infections were treated with antibiotics along with various preparations of ICS ranging from 176 to 1,000 μg/day and intermittent oral steroid bursts, approximately twice a year, for presumed asthma exacerbation during the previous 7 years. Her otolaryngology assessment revealed ‘empty nose syndrome’, and she was placed on saline and Wilson’s solution irrigation. A dynamic computed tomography (CT) scan of the chest (fig. 1a) revealed a significant difference in the caliber of the right main stem bronchus from 21 to 5 mm between inspiration and expiration, respectively. Mild focal bronchiectasis was noted in the right middle lobe along with bilateral parenchymal and pleural scarring. Repeat bronchoscopy revealed a dynamic collapse of the posterior tracheal wall. Intercartilaginous spaces were deeper than usual with multiple mucosal crypts involving the posteromedial wall of the left main bronchus, findings that are suggestive of smooth muscle atrophy. The medial end of the right main stem bronchus cartilages were separated from the posterior wall, which supports our notion of SMAS. The TB-SMAS area was covered only by bronchial mucosa; yet, no mediastinal structures were seen (fig. 1b, c). The pulmonary function tests were normal, and her methacholine challenge was also negative. Her immunodeficiency evaluation was unremarkable. She was recommended tracheobronchopexy but opted for a second opinion at a different institution and was lost to follow-up. Her death was confirmed in 2012.

Case 2
A 62-year-old female ex-smoker and recipient of a left single lung transplantation for severe COPD underwent a bronchoscopy 3 weeks following treatment for A1B1 acute cellular rejection. She also had a history of hypothyroidism, hyperlipidemia, and hypertension. She had accumulated 33 pack-years of smoking, prior to quitting it in the year 2000. She had been on various doses of inhaled fluticasone for the past 13 years ranging from 220 to 1,000 μg/day. She had occasionally received systemic steroid bursts prior to 2012, but since then she was kept on prednisone 5 mg daily. She received a left single lung transplantation in December 2013. In January 2014, a surveillance bronchoscopy revealed A1B1 rejection, for which she was treated with a high dose of systemic steroids.

Fig. 1. a CT of the chest at the level of the carina revealing marked bronchomegaly of the right main stem bronchus. b Airway examination at the main carina revealing the separation of the cartilaginous rings (arrow) from the posterior tracheal wall (inspiration). c During exhalation, a >50% reduction is observed in the airway lumen consistent with EDAC.

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Her pre-transplant medications included albuterol inhaler, tiotropium bromide, ICS, and oral prednisone 5 mg daily. Her post-transplant medications included albuterol, fluticasone-salmeterol, tiotropium bromide, prednisone, tacrolimus, sulfamethoxazole-trimethoprim, itraconazole, valganciclovir, and aspirin.

A CT scan prior to the transplant revealed excessive dynamic airway collapse (EDAC) during expiration (fig. 2a). Flexible bronchoscopy revealed a separation of the left posterior tracheal wall from the cartilaginous rings (arrow) on the left airway examination and histopathology. c HE stain of explanted lung bronchi revealing the total absence of ASM. C = Cartilage; CT = connective tissue; G = mucosal glands.

Case 3
A 65-year-old female ex-smoker with a history of diabetes, hypothyroidism, and very severe COPD diagnosed in 2000 was also treated with various doses of ICS ranging from 176 to 1,000 μg/day since then and placed on 5 mg prednisone since 2005. She underwent sequential bilateral lung transplantation in 2009 with a fairly stable post-transplant course. After the transplantation, she was maintained on ICS, tacrolimus, azithromycin, low-dose prednisone, azithromycin, and sulfamethoxazole-trimethoprim. She developed bronchiolitis obliterans syndrome following the transplantation. In September 2014, she underwent flexible bronchoscopy for evaluation of chronic cough and further decline in FEV1. There was no evidence of infection or acute rejection. However, bronchoscopy revealed a complete separation of the posterior bronchial wall from the right lateral cartilaginous ring cov-
ered with mucosa. This was also associated with a dynamic airway collapse during expiration, again supporting the notion of TB-SMAS (fig. 3; online suppl. video 1; see www.karger.com/doi/10.1159/000431381).

Case 4
A 57-year-old male ex-smoker presented with a worsening productive cough and dyspnea of 2 years’ duration. He had a history of hypertension, obstructive sleep apnea, and sinopulmonary infections for 30 years, and bronchiectasis and bronchomalacia for the past 10 years. Six years ago, a self-expanding metallic stent was placed in his left main stem bronchus for his tracheobronchomalacia at an outside institution, and since then, he had undergone repeated endobronchial laser photosection for excessive granulation of tissue. Over 10 years, he was treated with intermittent bursts of systemic steroids and inhaled fluticasone ranging from 220 to 2,640 μg/day for his symptoms of dyspnea which was thought to be due to COPD. His latest CT of the chest revealed tracheomegaly with an excessive dynamic collapse of the posterior tracheal wall producing near-total collapse of the tracheal lumen during expiration from the level of the manubrium to the carina. Bronchoscopy also revealed severe tracheobronchomalacia as well as excessive dynamic posterior wall collapse (EDAC). Once again, the depth of intercartilaginous spaces was increased, and mucosal crypts involving the posteromedial aspect of both main bronchi suggested loss of muscle fiber. The posterior walls of both main bronchi were separated from the medial ends of the cartilaginous rings. The patient underwent tracheostomy with a "T" tube placement with the distal end extending up to the carina (fig. 4).

Discussion

Posterior tracheal wall or pars membranacea is a smooth muscle structure connecting the ends of tracheobronchial cartilages. Hence, it provides the structural integrity and dynamics to the tubular tracheobronchial tree. For the first time we have encountered ASM atrophy associated with the loss of attachment of the posterior muscular wall from the ends of the C-shaped cartilages. The etiology of TB-SMAS remains a speculation; yet, we hypothesize that it may be multifactorial. The following is the information available on TB-SMAS and a discussion of other disease entities that share similar findings.

Tracheomalacia
Excessive dynamic collapse and tracheomalacia are the weakness of the trachea that is felt to be secondary to a reduction in the longitudinal elastic fibers of the pars membranacea [1–4], or impaired cartilage integrity, respectively [5]. In adults, this can be related to hereditary causes such as Mounier-Kuhn syndrome and idiopathic giant trachea, but it is more commonly due to secondary causes including trauma, post-intubation or post-tracheostomy injury, emphysema, chronic infection/bronchitis, chronic inflammation; relapsing polychondritis, smoking, and chronic external compression of the trachea due to tumor, abscesses, cyst or vascular anomalies such as vascular rings and aneurysms. The clinical features of this condition are nonspecific and include dyspnea, cough, sputum production, and hemoptysis. These are often ascribed to other conditions such as emphysema, asthma,
chronic bronchitis, or cigarette smoking. Tracheomalacia can be suspected by CT imaging and confirmed by bronchoscopy. Both TB-SMAS and tracheomalacia can lead to an obstructive pattern on pulmonary function testing. However, the characteristic separation of the posterior tracheal wall from the ends of the C-shaped tracheal cartilages is only seen in TB-SMAS [1].

**Atrophic Bronchitis (Deformans)**

Primary dystrophic and primary inflammatory bronchopathies are the two distinct forms of the chronic atrophic process in the bronchial mucosa. Primary dystrophic bronchopathy presents structurally and functionally as dystrophy of the bronchial mucosa in combination with sclerosis of the lamina propria. This is felt to be due to a significant decrease in the synthetic processes in bronchial epitheliocytes. The primary inflammatory form of atrophic bronchitis has clinical symptoms typical for the inflammatory process and is characterized by gradual reorganization of the bronchial wall and by maintaining a sufficiently high level of metabolic reactions in bronchial epitheliocytes [6]. Although atrophy of the smooth muscle wall is common to atrophic bronchitis and TB-SMAS, the characteristic separation of the posterior tracheobronchial smooth muscle wall from the ends of the cartilages is not seen in atrophic bronchitis. Second, the TB-SMAS is limited to the large airways, including the trachea and major bronchus, whereas atrophic bronchitis mainly involves the medium to small-sized airways, i.e., the bronchus and its smaller subdivisions. As a result, TB-SMAS leads to the dynamic collapse of the tracheal lumen, a feature that is not described in atrophic bronchitis.

**Bronchial Diverticuli**

Wang and Ying [7] investigated the morphogenesis of the bronchial diverticulum using an electron microscope and found submicroscopic depressions and dilatation of the bronchial gland ducts on the mucosal surface. These multiple depressions are believed to be fused to form a diverticulum which herniates through the bronchial smooth muscle. They felt that a number of conditions including chronic cough may weaken the bronchial wall and cause bronchial diverticulosis. They also pointed out that the latter is not confined to patients with COPD but can also be found in other lung disorders and is therefore not the hallmark of irreversible lung disease. Bronchial diverticulosis should be looked for during bronchoscopy since it can be a harbinger of chronic infection. The bronchoscopy in our patients was unrevealing for any diverticuli.

**Airway Remodeling**

The changes that are typically observed in chronic bronchitis or COPD are not consistent with the endobronchial smooth muscle atrophy and separation described in our patients. The typical pathological findings in airway remodeling are squamous metaplasia without significant thickening of the reticular basement membrane, bronchial goblet cell hyperplasia and submucosal gland enlargement. In contrast to asthma, hypertrophy of the smooth muscles is not observed in the large airways of patients with COPD. There is, however, smooth muscle hypertrophy in the distal airways, and this was found to correlate with the degree of obstruction [8, 9]. Since our observations are not seen in the majority of patients with COPD, it may not be a consequence of the ‘remodeling’ or the pathological changes that are believed to occur in most patients with COPD. Moreover, remodeling is mainly limited to the distal airways, whereas TB-SMAS involves the proximal airways leading to the excessive dynamic collapse of the tracheal lumen. Therefore, we believe that TB-SMAS is entirely different from airway remodeling observed in chronic bronchitis and/or COPD patients.

**Mounier-Kuhn Syndrome**

Mounier-Kuhn syndrome, also referred to as idiopathic giant trachea or tracheobronchomegaly, is a condition characterized by a significant enlargement of the trachea and large bronchi. This results in the inability of individuals to effectively clear their secretions. Pooling of secretions creates conditions for recurrent lower respiratory tract infections and the development of bronchiectasis [10]. This condition was first described endoscopically and radiographically by Mounier-Kuhn in 1932 [11]. It is a rare disease of unknown etiology, although there have been reports of familial occurrence. Pathological findings include atrophy of the longitudinal elastic fibers and thinning of the muscularis mucosa. Management of the condition is geared towards facilitating the clearance of airway secretions, and this consists primarily of chest physiotherapy. Antibiotics are used in the case of infection, and stenting is sometimes used in advanced cases [12]. The main difference between Mounier-Kuhn syndrome and TB-SMAS is their endoscopic appearance as well as the association of Mounier-Kuhn syndrome with recurrent infections. On bronchoscopy, Mounier-Kuhn syndrome is associated with diverticulosis in the trachea and bronchi. On the other hand, TB-SMAS patients do not have tracheobronchomegaly or diverticuli.
Proposed Mechanism for TB-SMAS

Based on our clinical observations, we believe that the frequent and long-term use of potent or high-dose ICS may cause TB-SMAS in these patients. There is ample data showing that steroid use can cause both skeletal and smooth muscle atrophy either by decreasing protein synthesis or by its catabolic effects on muscle tissue [13–16]. It is also well documented that ICS leads to the inhibition of ASM proliferation among patients with airway inflammation [17–19], and it may also reverse the hyperplasia and hypertrophy of ASM seen with airway remodeling [20]. An in vitro study by Fernandes et al. [17] showed that dexamethasone significantly attenuated effects of various mitogens on ASM proliferation. They suggested that this might be one of the ways in which ICS results in an improvement in asthmatics. Pavlovic et al. [21] showed that steroids given systemically can result in tracheal smooth muscle atrophy and reduction in the number of tracheal epithelial cells in rats. Although there is no data on humans, this is one of the possible mechanisms of bronchial smooth muscle atrophy in patients on chronic ICS or systemic corticosteroids. It is well established that the antiproliferative effects of corticosteroids are mediated via several different pathways that eventually lead to a reduction in different cytokines and growth factors in the airway [22]. However, many of these cytokines and growth factors also have key physiological roles in healing and repair in the airway [23]. It thus seems plausible that the use of ICS in the airway over a long period of time may lead to adverse effects on ASM by impairing some of the repair mechanisms which are physiologically driven by the growth factors suppressed by ICS administration.

Another important topical action of corticosteroids is their vasoconstrictive effect. This has in fact been utilized in the McKenzie skin-blanching test to assess the in vivo ‘potency’ of ICS [24]. The same principle is also utilized to compare the efficacy of different ICS by measuring the airway blood flow in humans [25–27]. Furthermore, it has been consistently demonstrated that these effects are present in both asthmatic and non-asthmatic subjects, the magnitude being larger among asthmatic patients [27, 28]. All these effects are considered favorable for ameliorating airway inflammation. However, there is a lack of data examining the long-term effects of repeated episodes of vasoconstriction on ASM. It would seem reasonable to be concerned about ischemia of ASM given the frequent vasoconstrictive episodes. These negative effects may be compounded by a lack of adequate repair and healing of ASM which may accompany the use of ICS as discussed above. Over a long period of time, these effects may combine to cause a progressive weakness of the airway musculature eventually leading to TB-SMAS. It is pertinent to note here that these potential adverse effects are difficult to recognize in clinical trials as their development likely takes years of regular use of ICS. All patients presented in this report had been on long-term ICS for at least 7 years.

Recently, ICS have also been found to be associated with a higher incidence of pneumonia and mycobacterial infections [29–31]. If present, these chronic infections would also have adverse effects on ASM. There was no evidence of such an infection in our patients.

Gastroesophageal reflux disease with chronic aspiration, recurrent infections and chronic bronchitis with related cough, beta-agonists and Mucomyst use may be other potential contributors, although there is no evidence to support their association. We strongly believe that the use of ICS is related to ASM atrophy and contributes to TB-SMAS. Although this association is largely speculative at this stage, it appears to have a sound biological basis. Future studies aimed at further evaluating the association of ICS with TB-SMAS and elucidating underlying mechanisms should be considered.

Conclusion

Our TB-SMAS patients demonstrated features of bronchial smooth muscle atrophy and separation due to unknown etiology. As evident on bronchoscopy and CT images, TB-SMAS causes airway collapse and may lead to airway obstruction in these patients. TB-SMAS also carries a risk of rupture of the trachea especially in patients undergoing rigid bronchoscopic interventions. Therefore, potential prevention and early diagnosis of TB-SMAS has a major clinical significance. Future studies aimed at evaluating the association of ICS with TB-SMAS and elucidating the underlying mechanisms should be considered.

References


