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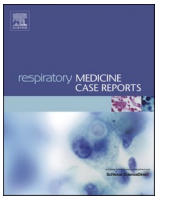

Case Report

Augmentation therapy with human alpha-1-proteinase inhibitor reduces exacerbations in patient with bronchiectasis and alpha-1-antitrypsin deficiency

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ABSTRACT

Alpha-1-antitrypsin deficiency (AATD) is a rare cause of noncystic fibrosis (CF) bronchiectasis. The benefits of augmentation therapy in patients with chronic obstructive pulmonary disease (COPD) and pulmonary emphysema are well established. The role of augmentation therapy in AATD bronchiectasis in patients without pulmonary emphysema is not clear.

We present the case of a 53-year-old woman (never smoker) who presented with increased susceptibility to infection, productive cough, and intermittent hemoptysis. Pulmonary function testing revealed restrictive impairment [VC 2,7 l (83% of pred.), FEV1 2,3 l (86% of pred.)]. A CT scan of the chest showed marked basal bronchiectasis with mucoid impaction, surrounding consolidation, and no emphysema. Despite frequent use of inhalation therapy, a satisfactory control of symptoms and exacerbations was not achieved.

In the course of extended diagnostics regarding the genesis of bronchiectasis, a reduced alpha-1-antitrypsin (AAT) serum level was detected, and a genetic test revealed a homozygous Pi*ZZ genotype. We started augmentation therapy with AAT (Respreeza®, CLS Behring) at the dose of 60 mg/kg per week; the therapy was well tolerated by the patient, and she reported clinical improvement with a reduction in exacerbation frequency.

AAT is a serine protease inhibitor and plays a major role in regulating inflammatory activities, in particular by inhibiting neutrophil elastase (NE). The present case illustrates the positive effect of augmentation therapy, including patients without airway obstruction. Among other causes, AATD should be considered as a possible cause of bronchiectasis, and the effects of augmentation therapy for this indication need to be prospectively studied.

Abbreviations

AAT Alpha-1-antitrypsin

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AATD	Alpha-1-antitrypsin deficiency
BAL	bronchoalveolar lavage
COPD	chronic obstructive pulmonary disease
CF	cystic fibrosis
CT	computed tomography
DLCO	diffusion capacity of carbon monoxide
ERS	European Respiratory Society
FEV1	forced expiratory volume in 1 second
GVHD	graft-versus-host disease
IL	Interleukin
LTB4	leukotriene-B4
NE	neutrophil elastase
pred	predicted
TNF-α	Tumor Necrosis Factor-α
VA	alveolar volume
VC	vital capacity

1. Introduction

Alpha-1-antitrypsin (AAT) deficiency is a genetic disease caused by mutations in the SERPINA1 gene. The serine protease AAT is mainly secreted by hepatocytes, but it is also synthesized in pulmonary alveolar cells, intestinal cells, neutrophils, macrophages, and the cornea [1]. AAT plays a major role in regulating inflammatory activities, particularly by inhibiting neutrophil elastase (NE).

The most common genotype in severe AATD results from the homozygous point mutations Glu342Lys (the Z allele) [1,2]. The majority of the mutant AAT is degraded within the endoplasmic reticulum of hepatocytes [3], with only a fraction of it reaches the lungs. Additionally, the mutant Z AAT is less effective in inhibiting NE [4] and tends to form polymers [5,6] with proinflammatory potential [7].

AATD patients typically present with emphysema and airways obstruction and may develop liver cirrhosis. However, less frequent manifestations include bronchiectasis.

2. Case report

A 53-year-old female patient presented with productive cough, intermittent hemoptysis, and 3–4 infections per year. Dyspnea both at rest and at exertion were denied. She had never smoked, and apart from hypothyroidism and varicosis, there were no known pre-existing conditions.

On physical examination coarse crackles could be auscultated, predominantly over the left lung. Performing body plethysmography revealed a restrictive lung disease with a vital capacity (VC) of 2,7 L (83% of predicted), a forced expiratory volume in 1 s (FEV_1) of 2,3 L (86% of predicted), and a Tiffeneau index of 85% of predicted. The diffusion capacity of carbon monoxide (DLCO) was 80% of predicted, and the ratio of DLCO to alveolar volume (VA) was 88% of predicted, thus indicating no relevant signs of diffusion impairment related to alveolar volume. Computed tomography (CT) of the chest showed basal-predominant bilateral bronchiectasis with bronchial wall thickening and mucoid impaction and surrounding consolidation (shown in Fig. 1). There was no evidence of emphysema, even in quantitative CT.

After exclusion of more frequent causes for bronchiectasis, laboratory testing showed a reduced AAT serum level of 30 mg/dl. C-reactive protein was within the normal range. The patient's results were consistent with those for a Pi*ZZ phenotype and genotype.

In the further course, no clinical stabilization could be achieved under regular inhalations with hypertonic saline solution. We therefore applied to the responsible health insurance company for the implementation of augmentation therapy with AAT

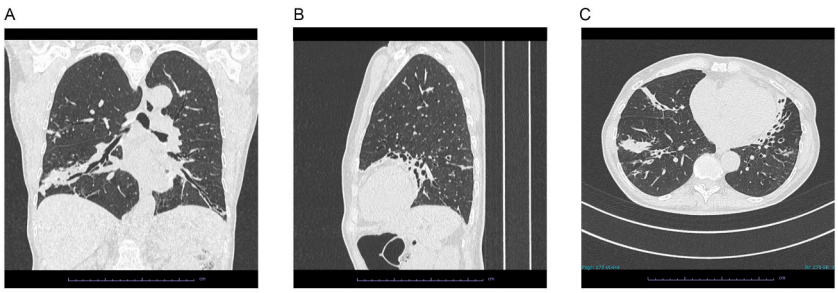

Fig. 1. Thin-sliced CT scan of the lungs in coronal (A), sagittal (B), and axial (C) planes. The predominant finding was basal-predominant bilateral bronchiectasis with bronchial wall thickening, mucoid impaction, and surrounding consolidation without emphysema.

(Respreeza®, CSL Behring) as an off-label use. The application was approved so that we could initiate intravenous augmentation therapy with human plasma AAT in a weekly dosage of 60 mg per kg body weight. Under augmentation therapy, serum AAT levels normalized and lung function stabilized. In addition, the frequency of exacerbations decreased significantly, and the clinical condition improved. The patient tolerated the therapy very well, and after a few months, he was possible to switch to home-based self-administration without any problems.

3. Discussion/conclusion

The data concerning the association between bronchiectasis and AATD is contradictory. Some authors describe a higher frequency of bronchiectasis in patients suffering from AATD [8–11], and Araujo et al. reported that the severity of AATD correlated with the severity of bronchiectasis [12]. However, there are also reports that AATD and bronchiectasis do not correlate [13–15]. Also, there is high a prevalence of bronchiectasis in COPD patients [16], which can be a potential confounder [17].

Whilst there is currently no proof that AATD causes bronchiectasis, it is reasonable to think that the lack of AAT and therefore the lack of its anti-inflammatory properties may cause bronchial wall inflammation and eventually result in bronchiectasis. Patients with a Pi*ZZ genotype have a higher risk of bacterial infections [18]. Peppers et al. studied patients with humoral deficiencies obtaining immunoglobulin replacement therapy and reported that AAT levels were lower in patients with bronchiectasis compared to those patients without bronchiectasis [19], suggesting a role for AAT in the pathogenesis of bronchiectasis. There are three ways in which the proinflammatory effect of AATD could cause bronchiectasis: through the interaction of AAT with proinflammatory cytokines, through increased activity of NE, and through AAT polymers.

AAT can modulate the activity of neutrophils via inhibition of caspase-3 [20]. Additionally, AAT can significantly lower Tumor Necrosis Factor-α (TNF-α) [21], Interleukin-8 (IL-8) [21], and IL-1β [22] levels and can reduce the chemoattractant effect of IL-8 [23] and leukotriene-B4 (LTB4) [24] by directly binding these substances.

In AATD patients, the activity of NE is less antagonized promoting inflammation. The proteolytic activity of NE has been shown to reduce the extracellular immune response [25,26]. Also, NE-mediated expression of cell surface mucin (MUC1) promotes bacterial internalization in epithelial cells reducing their exposure to the immune system [27]. In a prospective cohort study of Chalmers et al., it was shown that elastase activity in sputum was significantly associated with the bronchiectasis severity index, radiological extent of bronchiectasis, and a higher rate of exacerbations in the 3-year follow-up [28].

As mentioned, the polymers formed by the Z isoform of AAT have further proinflammatory potential [7]. There is evidence that especially the ZZ phenotype is associated with severe bronchiectasis and higher rates of exacerbations and hospital admissions [12].

The only disease-specific treatment for AATD is augmentation therapy with human-derived AAT, which is a safe and well-tolerated therapy [29]. It has been shown that this treatment significantly reduces loss of lung density and therefore disease progression in patients with lung emphysema and AATD, which relates to mortality in AATD patients [30,31]. AAT augmentation therapy also reduces proinflammatory immune processes. It was demonstrated that the inflammatory activity in plasma and bronchoalveolar lavage (BAL) fluids of AATD patients receiving augmentation therapy decreased under therapy [32]. Zhu et al. investigated rats with Ventilator-Induced Lung Injury and found that intravenous administration of AAT reduced the levels of proinflammatory cytokines while increasing the level of anti-inflammatory cytokines in the BAL fluid [33]. Similarly, it was shown in mouse models of graft-versus-host disease (GVHD) that administration of AAT reduced proinflammatory cytokine levels [34].

Currently, there are no trials that demonstrate a clinical improvement or slowing of progression in bronchiectasis patients with AATD receiving augmentation therapy. However, this case report shows that some AATD patients with bronchiectasis can benefit from augmentation therapy. To identify these patients, it is paramount to screen bronchiectasis patients for this genetic disease. However, at present the European Respiratory Society (ERS) and the British Thoracic Society do not recommend screening for AATD in bronchiectasis patients without emphysema [35,36].

Statement of ethics

Ethics committee approval was not sought for this study because the University of Heidelberg does not require ethical approval for reporting individual cases. This study was completed in accordance with the Helsinki Declaration as revised in 2013.

Written informed consent was obtained from the patient described for their anonymized information to be published in this article.

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None.

Author contributions

EB and FCT wrote the first draft of the manuscript. KS interpreted the radiological exams. MAP, JB, MV, and FJFH provided the patient data. All authors read and approved the final version of the manuscript.

Data availability statement

The data of this study are available from the corresponding author on reasonable request.

Declaration of competing interest

Emanuel Buck reported advisory fees from CSL Behring. Franziska C. Trudzinski reported personal fees from GlaxoSmithKline, Novartis, CSL Behring, and Grifols outside the submitted work. Judith Brock reported personal fees from Streamed up!, AstraZeneca, and Boehringer Ingelheim outside the submitted work. Maria A. Presotto, Kai Schlamp, Martina Veith, and Felix F.J. Herth have no conflicts of interest.

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