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Case Report

Patient with Combined Asthma and Bronchiectasis Secondary to Alpha-1 Antitrypsin Deficiency: Case Report and Review of Literature

Antonella Spacone FCCP*

Respiratory Medicine Department, Hospital "Santo Spirito" Pescara, Pescara, Italy

***Corresponding Author:** Antonella Spacone FCCP, Respiratory Medicine Department, Hospital "Santo Spirito" Pescara, Pescara, Italy.

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Abstract

Background: Alpha-1 Antitrypsin Deficiency (AATD) is a genetic disorder that predisposes one to pulmonary and liver disease.

It is characterized by decreased serum concentrations of a glycoprotein (alfa 1 antitrypsin) that is synthesised and secreted primarily by hepatocytes into the bloodstream. Lung tissue is the principal target of this protein and it is crucial that the protease-antiprotease balance be manteined. The classical pulmonary presentation of AATD is severe, early-onset pan-acinar emphysema but there are associatios between AATD and bronchiectasis and, although it is controversial, between AATD and asthma.

Although AATD is common in populations of European ancestry, it remains underdiagnosed due to its variable clinical presentation and poor physician knowledge of its varying presentations.

Case Report: This case report of a patient with allergic asthma and bronchiectasis, and subsequently, the diagnosis of AATD demonstrates the value of this screen when the 2 diseases are combined.

R.P., a 55-year-old female, non-smoker, with a diagnosis of allergic asthma from childhood, who had been treated with inhaled bronchodilators/corticosteroid association therapy and a leukotriene receptor antagonist from 10 years, presented with frequent exacerbations and worsening of bronchial obstruction and quality of life in the past 2 years; high-resolution computed axial tomography (HRCT) showed the presence of bronchiectasis. She underwent quantitative determination of blood AAT levels, supported by a qualitative test that detected SERPINA gene mutations, from which a profile of AATD emerged: a heterozygous P Lowell variant. Intravenous infusion of alfa-1 proteinase inhibitor introduced, with success.

This clinical case underscores the importance of considering the diagnosis of AATD in a nonsmoking patient with a combination of bronchiectasis and asthma and the benefit of augmentation therapy in reducing the number of exacerbations and improving quality of life.

Keywords: *Alpha-1 Antitrypsin Deficiency; Asthma; Bronchiectasis*

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a hereditary disease that increases the risk of chronic obstructive pulmonary disease (COPD in particular, emphysema), liver disease and several other conditions such as autoimmune disorders [1,2]. It is the most frequent hereditary disease that is diagnosed in adults with a prevalence of less than 5 cases per 10.000 habitans [3].

Severe AATD is an autosomal recessive disorder that is characterized by mutations in the SERPINA1 (also known as *PI*) gene, encoding for alfa 1 antitrypsin (AAT), a protein that inhibits neutrophil elastase (NE), an enzyme of the matrix component that targets elastine [4].

Alpha-1 antitrypsin (A1AT) is a 52-kDa, acute phase glycoprotein that is encoded by the protease inhibitor locus, located on the long arm of chromosome 14 (14q31-32.3). It comprises structure 7 exons, 4 coding (II, III, IV, and V) and 3 non-coding (IA, IB and IC).

More than 100 genetic variants of AATD have been described, with most cases resulting from homozygous inheritance of the Z allele. There is a significant heterogeneity with regard to pulmonary involvement in AATD.

The clinical pulmonary manifestations vary: the classical presentation of AATD is severe, early-onset pan-acinar emphysema with basilar predominance in adults [1,2]. In addition, a link of association between bronchiectasis and AATD with or without concomitant emphysema is supported by several studies [5,6]. The prevalence of asthma in the AATD population ranges from 4% to 45% [7-10]. In addition, an unusual association between most common deficitary alleles in AATD and idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) and pulmonary Langerhans cell histiocytosis has also been reported [11-13]. The condition can lead to pulmonary diseases, liver disease, rare multiorgan vasculitis, pancreatitis, necrotizing panniculitis and fibromyalgia [14-16].

The natural history of AATD in adulthood is often understood, causing significant morbidity and mortality in those who are affected. It is recognized in less than 10% of persons, and generally, its diagnosis is made after a pulmonary disease (in particular COPD) or liver disease has been identified after the deficiency has been diagnosed in a family member. Often, the poor knowledge and varying presentation of this condition are obstacles even to physicians.

Treatments with purified A1AT preparations, obtained through pooled human plasma (augmentation therapy), improve survival and disease-related quality of life and slow the progression of organ damage [1,2].

This case illustrates the importance of considering diagnosis of AATD in a nonsmoker with combined asthma and bronchiectasis to optimize the treatment for the patient with augmentation therapy.

Case Report

R.P. a 55-year-old female (nonsmoking body mass index: 29 Kg/m^2) with a diagnosis of allergic asthma (skin prick test positive for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) from childhood, just treated with inhaled bronchodilators/corticosteroid association therapy and leukotriene receptor antagonist from 10 years, was admitted to our Respiratory Medicine Care Unit for persistent cough that was accompanied by dyspnea and low-grade fever. Her physical examination revealed pulmonary auscultation that was remarkable for a prolonged expiratory phase with rhonchi.

Her pulmonary function testing (PFT) showed a moderate obstruction pattern: forced vital capacity (FVC) was 2.30 lt - 91% predicted, forced expiratory volume 1s (FEV1) was 1.20 lt - 56% predicted, the FEV1- FVC ratio was 0.61 with positive bronchodilator response and the carbon monoxide diffusing capacity wasf 60%. She had history of wheezing, atopy, frequent exacerbations and in the past 2 years progressive worsening of bronchial obstruction and quality of life. Table 1 shows the PFT values from the last 3 years.

	Year 2017	Year 2018	Year 2019
FVC	2,40 lt - 94% pred	2,30 lt - 90% pred.	2,30 lt - 91% pred.
FEV1	1,68 lt - 74% pred.	1,40 lt - 65%	1,20 lt - 56% pred.
IT	0,70	0,68	0,61
DLco	72%	68%	60%

Table 1: *Values of pulmonary function test.*

FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume 1s; DLco: Carbon Monoxide Diffusing Capacity.

During these evaluations, she was also subjected to Saint George's Respiratory Questionnaire (SGRQ) the scores of which were respectively 55-60-78. The questionnaire consists of 76 items that are divided into 3 parts measuring symptoms, activity limitations and social

and emotional impact of the disease. Each item is given a weight determined by the degree of distress for each symptom or state. Overall scores range from 0 (no effect on quality of life) to a maximum of 100 (maximum perceived distress); thus, a higher score indicates a poorer quality of life.

The arterial blood gas analysis was normal.

High-resolution computed axial tomography (HRCT) showed lingular and bilateral basal bronchiectasis (Figure 1). She presented with increased serum immunoglobulin (Ig) E, others Ig A- M- G and precipitating IgG antibodies against fungal or avian antigens and immunological tests and liver enzymes were in the normal range. The abdominal ultrasonography was normal. Sweat test to rule out cystic fibrosis was negative. The microbiological analysis of sputum indicated the presence of Pseudomonas aeruginosa at 1.000.000 ufc/mL. She was treated for this exacerbation with antibiotic therapy and systemic corticosteroid. Plasma protein electrophoresis with quantitative determination of alfa1- globulin was performed: quantitative serum A1AT assay showed an average AAT concentration of 88 mg/dL (normal value 90 - 200) and protein phenotyping using isoelectric focusing (IEF) and genotype analysis revealed the presence of heterozygosity P Lowell.

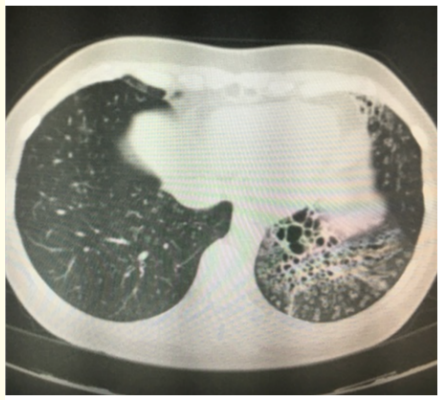

Figure 1: *Images of high-resolution computed axial tomography (HRCT).*

After resolving the acute disease, augmentation therapy was begun with weekly intravenous infusion of pooled human plasma purified alfa 1-AT at 60 mg per Kg body weight. Treatament with bronchodilators and inhaled corticosteroid medications, was continued.

At the clinical follow-up 6 and 12 months after discharge, the FEV1 and DLco values on the PFT increased (Table 1). The patient did not experience any exacerbation and the quality of life better (SGQR 30).

The patient's relatives were subjected to genetic testing for AATD: the guys were negative.

Discussion

AAT deficiency remains an underdiagnosed disease because it is a rare condition, being an autosomal recessive disease, even if recent studies supports that this condition can be higher than expected [17].

Alfa 1 antitryspin is the most abundant serum serine protein inhibitor with anti- protease and immune-regulatory activities [18]. Usually it is considered and managed as common COPD but this case report shows the importance of considering this conditions, even in an obstructive pulmonary condition that differs from emphysema. The candidates for measurement of AAT levels are reported in table

2 [19]. The most common variants of AAT are PI S and PI Z [20]. The "P" phenotypic variant is associated with several genetic variants: one of this phenotype PI P (allele frequency in the German population) is the P Lowell variant, with the amino acid mutation Asp256Val in site III. Several studies have shown that the homozygotes of this PI type are at high risk of developing enphysema in particular [21,22].

1.	Patients with COPD
2.	Adults with bronchiectasis
3.	Patients with partial adult asthma
4.	Blood relatives of individuals with know AATD
5.	Dyspnea and chronic cough in many member of same family
6.	Liver disease of unknown cause
7.	Reduction in alfa-1 protein peak in the proteinogram

Table 2: *Subject to candidate for measurement of AAT test.*

This variant in heterozygous form was found in our case: the patient presented with combined asthma, non response to conventional treatment and and bronchiectasis. Although AATD is the most common hereditary disease in adults there is a generalized lack of knowledge in the medical community about this condition. Thus this genetic abnormality is grossly underdiagnosed worldwide. Early diagnosis is important, because it allows clinicians to implement early and interventions to treat the symptoms of the associated pulmonary diseases associated and exacerbations.

According to the literature data in this case report augmentation therapy reduces the frequency of acute exacerbations and improves the quality of life [23-25].

Deceleration or even interruption of disease progression is an important therapeutic objective.

Moreover, physicians must undertake family studies to ensure early diagnosis of other cases and provide genetic advice, if necessary, to identify and treat individuals who are affected by AAT deficiency in the earliest stages of disease [18].

Conclusion

According to the ERS and ATS statement, the management of AATD patients must be supervised by regional and national expert centers, because the clinical presentation can vary.

Increasing awareness among physicians is important in improving the diagnosis.

This case report shows also demonstrates the importance of a currect diagnosis of the case and the value of augmentation therapy in providing significant benefits with regard to the respiratory condition,

Although it is encouraging, this case report requires further confirmation by a more strict, prospective, randomized clinical trial.

Acknowledgments

None.

Conflict of Interests

All authors declare that they have no competing interests.

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