Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Respiratory Disease

Alpha-1-Antitrypsin Deficiency and Bronchiectasis: A Controversial Association (A Case Report)

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DOI: 10.36347/sjmcr.2022.v10i05.010 | **Received:** 14.04.2022 | **Accepted:** 10.05.2022 | **Published:** 17.05.2022

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Abstract **Case Report**

The association between Alpha-1-antitrypsin deficiency (AATd) and bronchiectasis is controversial: in fact, the literature shows opposite reports. Therefore, we present a case of this infrequent pulmonary manifestation in order to make it more familiar to clinicians. We will also investigate possible links between these two clinical entities, in order to highlight any cause/effect relationship.

Keywords: Alpha-1, Bronchiectasis, Controversial Association.

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INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a rare hereditary condition that leads to decreased circulating alpha-1 antitrypsin (AAT) levels, significantly increasing the risk of serious lung and/or liver disease in children and adults, where the emphysema is the main pulmonary manifestation and the association with AATd and bronchiectasis is controversial. Therefore, we present a case of this infrequent pulmonary manifestation in order to make it more familiar to clinicians.

PATIENT AND OBSERVATION

A 29-year-old nonsmoker female patient with a 10 years old medical history of shortness of breath and chronic cough with recurrent respiratory tract infections over the span of 10 years .She was also previously diagnosed and treated for whooping cough at the age of 10, and a right Pneumothorax at the age of 26.

The patient was referred to the respiratory diseases Department (ER) by her general practitioner (GP) due to worsening symptoms of a respiratory tract infection. A week prior, initial symptoms included a productive cough, fever and a mild dyspnea that were treated with antibiotics. On admission she complained of moderate dyspnea and productive cough, without chest pain, or hemoptysis. Her heart rate, blood pressure and Body temperature were normal, and she was fully alert and oriented. Pulmonary auscultation has revealed bilateral rhonchi and wheezes, a chest X-ray revealed multifocal, ill-defined bilateral consolidations. The CT scan showed extensive cylindric and varicose bronchiectasis affecting all lobes including the upper lobes (figure 1-2) without emphysema. Plethysmography had revealed an airways obstruction without signs of restriction. Carbon Monoxide Diffusing Capacity, PaO2 and PaCO2 were normal.

Sputum samples were collected before antibiotic administration and came back negative. Bronchoalveolar lavage (BAL) samples collected during bronchoscopy came back negative, and tuberculosis was ruled out after several test panels; mycological cultures turned out negative as well. Abnormalities in the lab results included an elevated C - reactive protein (CRP) level of 39,.7 [mg/l, positive > 5 mg/l], decreased serum Alpha 1 antitrypsin(Twice)(0,20g/l [lab norm (0, 9- 2 g/L).The sweat chloride was normal(34 mmol/L).

DISCUSSION

Alpha-1-antitrypsin is an endogenous protease inhibitor (Pi) of serine proteases coded by the serine-protease inhibitor (SERPINA1) gene and is secreted in the blood mainly by the liver. A deficiency in this

Protease inhibitor is a rare hereditary disease, showing a prevalence of 1–5 cases out of 10,000 [1-3].

There are several genetic pathological variants which are defined as deficient variants, dysfunctional variants or null mutations. These genetic variants may lead to an altered electrophoretic mobility of the resulting protein. These variants are labelled A–Z, i.e., faster or slower, compared to the most common (normal variant), labelled M [4, 5].

The most Common pathological variants are S and Z, with MM, MS, MZ, SS, SZ and ZZ protein phenotypes accounting for the majority of genotypes [1]. Chronic obstructive pulmonary disease (COPD) is the main thoracic manifestation associated with AATd [6].

Symptoms include a chronic cough, sputum, and progressive dyspnea with an evolution to chronic respiratory failure. Radiologically, the AATd is characterized with a panlobular emphysema predominantly in lower lobes, and early onset which is often out of proportion considering the patient's smoking history. The diffusing capacity of carbon monoxide (DLCO) and FEV1 are indicators for the presence, progression and severity of emphysema [1, 6].

The main extra-thoracic manifestations in AATd are liver disease with a possible evolution towards cirrhosis [1]. The determination of the serum levels of AAT confirms the Diagnosis, protein phenotyping by electrophoresis, and genotyping help to determine the responsible mutations.

On the other hand, bronchiectasis is a clinical syndrome characterized by a chronic cough, mucopurulent sputum production and recurrent respiratory infections, with abnormal and permanent bronchial dilatation in high-resolution computed tomography (HRCT). These findings may result from a number of possible causes, and these may influence treatment and prognosis.

The association between AATd and bronchiectasis is classecly controversial, but highly debated. A possible pathogenetic role of AATd in bronchiectasis etiology is suspected. The incidence of AATd among patients affected by bronchiectasis is higher, Chan *et al*. underline that [7]. In fact, AAT is involved in the regulation of different inflammatory pathways in the lung tissue, so that AAT deficiency would promote bronchial wall inflammation and damage, leading to bronchiectasis.

In particular, inhibition of serine proteases such as neutrophil elastase (NE), which is responsible for direct damage to lung epithelial cells and supportive tissues.

NE activity can also be interfering with bacterial clearance by the increased expression of a cell-surface mucin (MUC1) which is a bacterial binding site, promoting bacterial invasion into epithelial cells, Therefore, AAT anti-NE effect may promote bacterial killing by prolonging exposure of bacteria to such soluble extracellular anti-microbial mediators and phagocytic cells[8].

Moreover, some studies demonstrate that AAT seems to have immune-modulatory functions other than its classic anti-neutrophil protease activity [9]. In particular, Jonigk *et al*. [10] demonstrated that exogenous AAT, can significantly lower the lipopolysaccharide (LPS)-induced release of two molecules involved in different inflammatory pathways: Tumor Necrosis Factor-α (TNF-α) and Interleukin-8 (IL-8).

Bergin *et al*. [11] and O'Dwyer *et al*. [12] showed that AAT can directly bind IL-8 and leukotriene-B4 (LTB4), inhibiting their chemoattractant activities. AAT can also downregulates TNF-α gene expression by inhibiting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [13] and reduces LPS-induced synthesis and the release of active IL-1β [14], which is an important inflammatory mediator.

The pathogenetic role of AATd in the development of bronchiectasis can be also explained by the pro-inflammatory characteristics of mutated AAT isoforms secreted by the liver in blood and stored in lung tissue. In fact, the Z isoform of AAT could polymerize in the lung, acting as a chemotactic factor for neutrophils, with NE release leading to damage of the bronchial wall, and finally to bronchiectasis.

On the other hand, Shin *et al*. [15] found conversely that the frequency of the association between AATd and bronchiectasis is not important. Lonni *et al*. [16] demonstrates the same finding with a study that includes a population of 1258 bronchiectasis patients enrolled from different European countries; only eight cases of AATd (0,6%) are found.

CONCLUSION

An increasing number of studies suggest a pathogenetic role of AATd in bronchiectasis development, but the association is still controversial. A clearer response to this issue could help to improve the management of such disease.

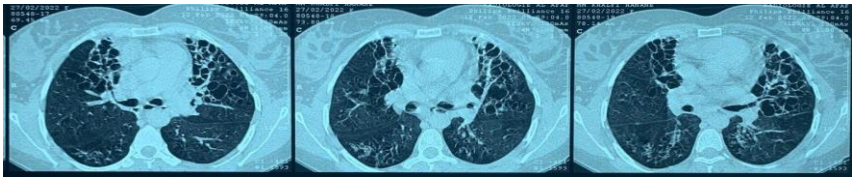

Fig-1: High-resolution CT scan slice shows bilateral and diffuse cystic bronchiectasis

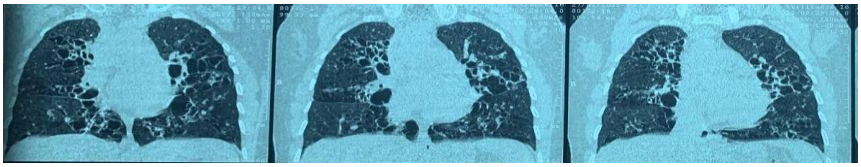

Fig-2: Sequential coronal images show extensive cystic bronchiectasis

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