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Case Report

Idiopathic Pulmonary Fibrosis Associated with Alpha1-Antitrypsin Deficiency: Concomitant Finding or Real Association?

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Abbreviations AAT: Alpha1-Antitrypsin; AATD: Alpha1-Antitrypsin Deficiency; CT: Computed Tomography; DLCO: Diffusion Capacity of Carbon Monoxide; ER: Endoplasmic-Reticulum; HRCT: High Resolution Computed Tomography; IPF: Idiopathic Pulmonary Fibrosis; mMRC: Modified Medical Research Council; NE: Neutrophil Elastase; PI: Protease Inhibitor; PR3: Proteinasi 3; UIP: Usual Interstitial Pneumonia

Abstract

Background: Idiopathic Pulmonary Fibrosis (IPF) is a chronic and progressive fibrotic interstitial lung disease of unknown etiology. It is unrelated to Alpha1-Antitrypsin Deficiency (AATD). Despite the progress in the pathogenetic knowledge, many aspects are still unclear. Lung fibrosis is actually regarded as a consequence of a chronic epithelial lung injury characterized by irreversible fibroblast activation and abundant amounts of collagens and other extracellular matrix substances deposition. Several proteins involved in oxidant/antioxidant balance and protease/antiprotease equilibrium have been associated with lung fibrogenesis, although AATD has never been clearly correlated with IPF development.

Case presentation: In this paper, we describe the history of twin homozygous sisters with a familiar homozygous Z type deficiency for Alpha1-Antitrypsin (AAT). One presented liver cirrhosis and the other twin sister developed IPF. This IPF patient with Z/Z mutation and very low AAT serum concentration had no signs of pulmonary emphysema, asthma or liver cirrhosis but she showed only radiological findings of IPF, and she started antifibrotic therapy.

Conclusion: An unusual association between the most common mutation in AAT (Z/Z mutation) and IPF development was reported in this letter supporting the hypothesis that antiprotease AAT maybe involved in IPF pathogenesis.

Introduction

Alpha1-antitrypsin deficiency (AATD) is a co-dominant inherited disorder characterized by the reduction of Alpha1-Antitrypsin (AAT), a serine protease inhibitor that is produced by hepatocytes and encoded by the Protease Inhibitor (PI) locus of the serpin 1 gene on chromosome 14q32.1 [1,2]. The normal plasma concentration of AAT ranges from 0.9 to 1.75 g/L (15-30 μM/L). Approximately 123 naturally occurring genetic variants of AAT have been discovered [3]. AATD-associated pulmonary manifestations include panacinar emphysema, bronchiectasis and rarely asthma [3-7]. Here we describe the history of twin homozygous sisters with a familiar homozygous Z type deficiency for AAT. A woman presented liver cirrhosis; the sister developed Idiopathic Pulmonary Fibrosis (IPF). This IPF patient with Z/Z mutation and very low AAT serum concentration (<15 μM/L) had no signs of pulmonary emphysema, asthma or liver cirrhosis but she showed pulmonary fibrosis. She was admitted to our hospital for persistent dry cough and progressive dyspnoea (mMRC 3). AATD diagnosis was made because her twin sister was affected by liver cirrhosis due to AATD with no pulmonary involvement. Our patient lived in Italy since she was 20 years old; her father was Spanish while her mother was French. At physical examination bilateral basal crackles were found. Blood gas analysis revealed PaO_2 53 mmHg that improved with 2 L/min oxygen therapy (PaO_2 64 mmHg). High Resolution CT (HRCT) of the lung showed patchy subpleural reticular abnormality mainly in the middle-lower lobes, associated with traction bronchiectasis and bronchiolectasis and multiple honeycomb-like lesions (Figure 1). Lung function tests showed a moderate restrictive dysfunction (FVC 90% pred.; FEV1 89% pred.) and reduction in carbon monoxide diffusion capacity (DLCO 46% pred.). The distance covered during six-minute walking test was normal with no oxygen desaturation. Assessment of autoantibodies and rheumatologic evaluation were negative. Based on the clinical history, physical examination and instrumental findings, a multidisciplinary group performed a diagnosis of IPF. The patient started treatment with Pirfenidone that was well tolerated

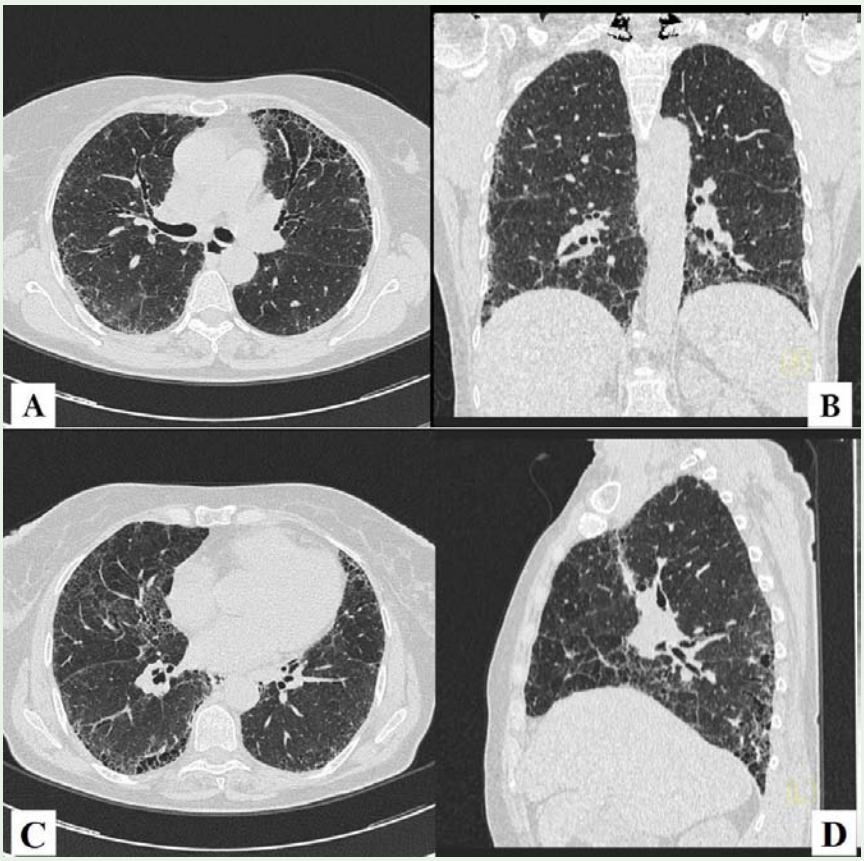

Figure 1: HRCT scans show coarse traction bronchiectasis in the anterior zone of left upper lobe associated with honeycombing (A), with thickening of inter and intralobular septa, especially in subpleural and basal lung areas (B). Honey combing pattern is highlighted with presence of subpleural cysts arranged on one or two files (C,D), predominate in the right apico-posterior lobe and in the lingula (C).

and stabilized the disease. Liver function has been closely monitored and no alterations were evidenced. Computed Tomography (CT) and Echo of the abdomen allowed to exclude liver disorders (Figure 2).

The most common mutation in AAT is the Z mutation. Of the mutated AAT, 70% are degraded by the endoplasmic-reticulum(ER) stress response in hepatocytes [1]. ER stress and accumulation of AAT in the liver leading to neonatal hepatitis, hepatic cirrhosis, and hepatocellular carcinoma in some Z/Z patients [1]. Indeed, one of the two sisters described presented severe liver cirrhosis as a consequence of AATD. In patients with AATD, the protease-antiprotease balance becomes skewed due to the degradation of mutant AAT by ER stress [1-3]. Neutrophil Elastase (NE) is the most important protease inhibited by AAT. When left unchecked, NE causes the destruction of lung matrix components, alveolar structures, and blood vessels. Mutant AAT has approximately 5 times less antiproteolytic activity against NE than normal [6,7].

The concomitant of IPF and AATD described in our case report is unusual. To date in the literature few data are available on this topic. Michalsky et al. [8] described an association between AATD and pulmonary fibrosis secondary to connective tissue lung diseases, such as rheumatoid arthritis and systemic sclerosis. Nowadays, available

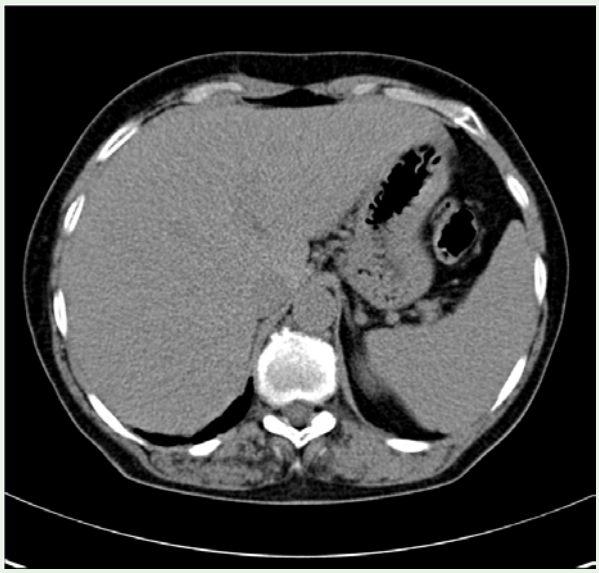

Figure 2: Axial CT scan of abdomen shows no signs of chronic liver disease. The liver appears in the limits for morphology and size, with regular margins. There are no signs of splenomegaly neither collateral circles.

literature reported only one case of concomitant AATD and IPF. The case report was published in 1996 in *Southern Medical Journal* and described an US family, in which both disorders were present but AATD was due to a heterozygous mutation [9]. Analogously, we describe this uncommon association in order to understand if severe AATD may be related with fibrosis development. Immunological studies have shown that Reactive Oxygen Species produced by neutrophils via the NADPH oxidase enzyme complex are eliminated by AAT through uncertain mechanisms [10]. AAT interferes with several mediators involved in IPF pathogenesis such as TNF-α, IL-1 antagonists, α-defensins, metalloproteinase's, cathepsins. These molecules are significantly over expressed in BAL and tissue from patients with IPF than controls [10]. Oxidative stress pathway and protease/antiprotease disequilibrium have been confirmed altered in the Pathophysiology of the disease.

In conclusion, we found an unusual association between the most common mutation in AAT and IPF development. AAT represents an antiprotease worthy of further investigation in IPF.

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