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Postponed diagnosis of alpha-1 antitrypsin deficiency

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Dear Editor,

Alpha-1 antitrypsin (A1AT) is a part of serine protease inhibitor family of proteins encoded by the SERPINA1 gene. A1AT function is inactivation of neutrophil-derived proteases, predominantly neutrophil elastase through destroying its structural integrity [1]. Alpha-1 antitrypsin deficiency (AATD) may lead to emphysema, liver disease, C-ANCA vasculitis, and panniculitis. Manifestation of the disease varies from asymptomatic to severe lung or liver disease.

The patient is a 65-year-old male with a major complaint of dyspnea, cough, and haemoptysis, who was for the first time hospitalized in our clinic. His dyspnea had been persistent and worsening in nature since he was diagnosed with chronic obstructive pulmonary disease (COPD) at age 50. Treatment with salmeterol/fluticasone 250/50 mcg 2 puffs twice a day via a hydrofluoroalkane inhaler did not provide benefit, and he required the use of salbutamol as a rescue inhaler multiple times per week. He had a 10 pack-year history of cigarette-smoking, but stopped five years ago. Evaluation of other systems was unremarkable. There was no prior family history of lung or liver disease. Medications at presentation included claritromicine 500 mg, two times per day, salmeterol/fluticasone 250/50 mcg 2 puffs twice a day, salbutamol as needed. Physical examination revealed bilateral wheezing, while the rest of the physical examination was unremarkable. He previously had numerous blood tests performed, including complete blood count, hepatitis serologies, HIV screening, TSH, Free T4, immunological tests (ANA, ANCA, ASMA, ANA HEp2, and AMA), which were all within normal limits. His ALT and AST levels at examination were slightly elevated for the first time in his medical history. Pulmonary function testing revealed an FEV1 (volume that has been exhaled at the end of the first second of the forced expiration) of 2.01 L (60% of predicted) with an FEV1/FVC ratio of 72%. He failed to demonstrate significant reversibility with salbutamol treatment (post-bronchodilator increase in FEV1 of 8%). He was found to have a reduced diffusing capacity of the lungs of 17.73 ml/min./mmHg (62% of predicted), and evidence of air trapping with a residual volume of 3.26 L (127% of predicted). The latter may have led to an artifactually low forced vital capacity (FVC) resulting in an FEV1/FVC ratio that was only mildly decreased. His pulmonary function tests over the past five years were also reviewed, and showed a 20.6% decrease in FEV1 over that time period, despite treatment with inhaled corticosteroids and long-acting bronchodilators. Abdominal ultrasound revealed inhomogeneous liver with otherwise unremarkable organs. Given the poor response to treatment and the early onset of COPD with a minimal smoking history, the diagnosis of A1ATD was considered. Serum testing for A1AT revealed a low level of 30 mg/dL (normal range is 100–190 mg/dL). A genotype analysis, performed at a commercial laboratory, was reported as ZZ genotype.

A1ATD is relatively common autosomaly recessive genetic disorder, caused by mutations of SERPINA1 gene. M alleles are normal, and have six subtypes: M1–M6. M1 is the most frequent subtype and is present in 95% of the population. Alleles with most severe clinical manifestations are Z alleles [1]. Diagnosing A1ATD can be demanding due to low recognition of the disease, genetic heterogeneity, and complexity of diagnosis. Its association with asthma or COPD is common, but even then the diagnosis is usually established late [2]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend screening of A1ATD to all symptomatic adults with COPD or asthma with an airflow obstruction that is not fully reversible after a bronchodilatators treatment. Also, children with a bleeding disorder or prolonged neonatal jaundice should be screened for A1ATD, as well as patients with cryptogenic liver cirrhosis [3]. At present, treatment of A1ATD is very limited. Only in the terminal stage of the lung or liver

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disease transplantation is a solution. Like with emphysema, patients with A1ATD can improve their symptoms with prolonged bronchodilators and corticosteroids. Once diagnosed, the prognosis of these patients is variable. It has been showed that FEV1 is the most important predictor of survival in patients with emphysema [4, 5, 6]. Patients without prior history of smoking, who had been diagnosed in family screening, have expected prognosis the same as healthy individuals [5].

We presented the case of a 65-year-old men whose serum levels of A1AT were below the low range, and ZZ genotype was confirmed. The delayed diagnosis of our patient seems to emphasize the need to remind the doctors about AATD, frequently associated with asthma or COPD symptoms. The low estimated prevalence of AATD prompted the establishment of a registry with the aim of learning more about the medical history and the quality of care of these patients.

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