A rare case of alpha 1-antitrypsin deficiency associated with hypogammaglobulinemia and recurrent pulmonary thrombosis

Raghav Gupta, Srilekha Sridhara, John A. Wood

Abstract:
Alpha 1-antitrypsin (AAT) belongs to the family of serpins (serine protease inhibitors). Loop sheet polymerization is the pathology behind serpinopathies which encompasses AAT, anti-thrombin III and neuroserpin deficiency. To the best of our knowledge, we report the first case of alpha 1-antitrypsin deficiency associated with hypogammaglobulinemia and recurrent pulmonary thrombosis without any concomitant use of drugs.

Key words:
Alpha 1-antitrypsin deficiency, hypogammaglobulinemia, recurrent pulmonary thrombosis, serpinopathies

A
lpha 1-antitrypsin deficiency (AATD) is an autosomal, co-dominant, hereditary disorder characterized by low enzyme levels in serum and lungs [Figure 1]. More than 3 million people worldwide have allele combinations (Z allele) associated with severe deficiency.[1] The main function of alpha 1-antitrypsin (AAT) is to inhibit neutrophil elastase. Proper conformation of AAT is essential for its function as an inhibitor. The Z variant, which is the most common AAT mutant, is associated with loop sheet polymerization leading to deficiency of the enzyme resulting in early onset emphysema and the concomitant medical conditions[2] [Figure 2].

Case Report
A 89-year-old, non-smoking, Caucasian woman with past medical history of AATD, recurrent pneumonias, dementia, diabetes mellitus and hypertension presents with productive cough and exertional dyspnea. During the seventh decade of her life, she was diagnosed with bronchiectasis and showed persistent decline of her health. She incurred recurrent pneumonias due to pseudomonas, empyema thoracis and mycobacterial infections and further laboratory investigation revealed AAT serum level of 24 mg/ml (83-199 mg/dl) with ZZ phenotype.

On admission, physical exam revealed she was febrile and had bilateral crepitations at the lung bases. Laboratory diagnostics revealed white cell count of 13.6 × 10^9/l with a differential of 80% neutrophils, 11% bands, 5% lymphocytes, 2% monocytes and 2% eosinophils. Liver function test include alanine transaminase of 27 U/l, aspartate transaminase of 28 U/l, alkaline phosphatase of 130 U/l, total bilirubin of 0.1 mg/dl, albumin of 3.1 g/dl and total protein of 5.6 g/dl. A chest radiography showed bilateral infiltrates followed with a chest computed tomography which revealed bilateral lower lobe segmental pulmonary arterial filing defects consistent with pulmonary emboli and marked emphysema with lower lobe cystic bronchiectasis and nodular infiltrates [Figure 3]. The patient was initiated on heparin and warfarin anticoagulation therapy along with the intravenous antibiotics of vancomycin 1 g every 12 h and cefepime 1 g every 12 h. Sputum cultures grew pseudomonas but acid fast bacilli, viral, fungal and blood cultures remained negative. An echocardiogram did not show evidence of endocarditis. Subsequently, patient showed remarked clinical and physiological improvement and antibiotic vancomycin was discontinued. Pulmonary function tests demonstrated severe obstructive lung disease with forced expiratory volume in 1 second (FEV1) of 37%, FEV1/forced vital capacity of 61% and total lung capacity of 121%.

Given the recurrent infections, immunoglobulin levels were checked and were suggestive of gamma immunoglobulin (IgG) of 514 mg/dl (normal 694-1618 mg/dl), immunoglobulin M of 30 mg/dl (normal 48-271 mg/dl) with normal immunoglobulin A of 270 mg/dl (normal 81-463 mg/dl). Antibody levels specific for capsular polysaccharides of Streptococcus pneumoniae and for tetanus toxoid were found low. She received monthly intravenous immunoglobulin infusions for immunoglobulin deficiency. Patient got discharged to home with oral anticoagulant warfarin and intravenous cefepime

Access this article online
Quick Response Code:
Website: www.thoracicmedicine.org
DOI: 10.4103/1817-1737.124442
for completion of total 14 days. During follow-up of the patient, her episodes of recurrent infections decreased relatively, however she continued to have pulmonary emboli. Her coagulation profile revealed protein C of 29 µ/dl (normal 75-165 µ/dl), anti-thrombin III of 85 µ/dl (normal 85-130 µ/dl) with negative factor V mutation, lupus anticoagulant and cardiolipin antibody.

Discussion

AATD, also known as hereditary emphysema, remains largely undiagnosed and commonly affects the lung, liver and rarely, skin. It is manifested by slowly progressive, moderate to severe panacinar emphysema that most often manifests in the third to fourth decades of life, resulting in a significantly lower life expectancy.

AAT is an acute phase protein produced in the liver, which limits the damage done to self-tissue during an inflammatory immune response. In particular, it has an inhibitory effect on leukocyte elastase produced by activated neutrophils.[3]

It is believed that up to 90% of the total AATD cases are undiagnosed as not all individuals develop symptomatic emphysema.[4] The emphysema associated with AATD is typically worse in the lower lung zones because protease: Protease inhibitor imbalance occurs in the lower respiratory tract.

Patients with persistent airflow obstruction on spirometry and unexplained dyspnea should be tested for AATD. Additional features that should lead to AATD testing include emphysema in a young individual (age equal to or less than 45 years), nonsmoker or minimal smoker, predominant basilar changes on the chest radiograph, a family history of emphysema and/or liver disease and current or prior unexplained chronic liver disease. The diagnosis of AATD is confirmed by low serum level of the enzyme and its deficient genotype. Treatment of AATD with emphysema remains supportive and includes smoking cessation, prompt treatment of lower respiratory tract and preventive vaccination. Lung transplantation is reserved for advanced emphysema.

Clinical findings or history of genetic linkage explains coexistence of AATD with hypogammaglobulinemia. Often patients with AAT deficiency are susceptible to recurrent bacterial infection affecting the respiratory tract, have an increased incidence of other infections, lymph node and splenic follicular hyperplasia.[5] AATD has been reported in two patients with common variable immunodeficiency.[6,7] Probable explanation of this

Figure 1: The human antitrypsin structure showing regular pattern of different sheets

Figure 2: Loop sheet polymerization causing serpinopathies

Figure 3: Chest computed tomography showed bilateral bronchiectasis in the lower lung zones and marked emphysema with lower lobe nodular infiltrates

Figure 4: Proximity of the gene coding of gamma immunoglobulin and alpha-1 antitrypsin enzyme
association is proximity of the gene coding of IgG and AAT resulting in hypogammaglobulinemia. The effectiveness of immunoglobulin replacement in patients with common variable immunodeficiency is immediately apparent with decreased annual incidence of pneumonia and hospitalization rates.

Vasculitis and increase coagulation factors in AATD are due to unchecked proteinase 3 activity as explained by linkage disequilibrium which leads to recurrent pulmonary emboli. Fiechtner et al. reported case of multiple pulmonary thromboemboli and pneumothorax secondary to AATD but was also associated with estrogen therapy. However, till date there are no studies demonstrating AATD, being the only entity behind pulmonary emboli. Our patient's coagulation profile revealed low protein C and borderline anti-thrombin III which explains increase proteinase activity by AATD. Although patient’s medical conditions including diabetes, hypertension and age related malnutrition leading to hypoprotenemia, are the possible risk factors for pulmonary coagulopathy, it is suggested that AATD with its increased proteinase activity leads to remarkable protein deficiency and more frequent episodes of pulmonary emboli.

We hereby, report for the first time, the unique association of AATD with hypogammaglobulinemia and recurrent pulmonary thrombosis. This case also signifies the identification of immunoglobulin deficiency in AATD patients. Further genetic insights into comorbidities are needed to manage the complex medical issues.

References

1. de Serres FJ, Blanco I, Fernández-Bustillo E. PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. Monaldi Arch Chest Dis 2007;67:184-208.
2. de Serres FJ, Blanco I. Prevalence of α1-antitrypsin deficiency alleles PPS and PZ worldwide and effective screening for each of the five phenotypic classes PMP, PMPZ, PPS, PPSZ, and PZZ. A comprehensive review. Ther Adv Respir Dis 2012;6:277-95.
3. Travis J, Salvesen GS. Human plasma proteinase inhibitors. Annu Rev Biochem 1983;52:655-709.
4. Silverman EK, Sandhaus RA. Clinical practice. Alpha 1-antitrypsin deficiency. N Engl J Med 2009;360:274-57.
5. Spickett GP, Misbah SA, Chapel HM. Primary antibody deficiency in adults. Lancet 1991;337:281-4.
6. Phung ND, Kubo RT, Spector SL. Alpha 1-antitrypsin deficiency and common variable hypogammaglobulinemia in a patient with asthma. Chest 1982;81:112-5.
7. Phung ND, Harbeck RJ, Helbling-Muntges C. Familial hypogammaglobulinemia. Genetic linkage with alpha 1-antitrypsin deficiency. Arch Intern Med 1983;143:575-7.
8. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann Intern Med 1980;93:55-6.
9. Fiechtner JJ, Magnin GE. Multiple pulmonary thromboemboli and pneumothorax. Complications of exogenous estrogen in an alpha-1-antitrypsin deficient woman. Wis Med J 1978;77:S103-6.

How to cite this article: Gupta R, Sridhara S, Wood JA. A rare case of alpha 1-antitrypsin deficiency associated with hypogammaglobulinemia and recurrent pulmonary thrombosis. Ann Thorac Med 2014;9:39-41.

Source of Support: Nil, Conflict of Interest: None declared.