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# Unique Case of Alpha 1-Antitrypsin Deficiency Causing Decreased Protein-C and S Activity Leading to DVT and Pulmonary Embolism

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## Abstract

Although Alpha-1 Antitrypsin Deficiency (AATD) is generally considered to be rare, estimates that 80,000 to 100,000 individuals in the United States have severe deficiency of AAT suggest that the disease is under-recognized. The prevalence of AAT varies considerably from one country to another; however, it is estimated that more than 3 million people worldwide have allele combinations associated with severe deficiency of AAT

The pathogenesis of the liver disease is quite different and is called a "toxic gain of function." The liver disease results from the accumulation within the hepatocyte of unsecreted variant AAT protein. Only those genotypes associated with pathologic polymerization of AAT within the endoplasmic reticulum of hepatocytes (eg, PI*ZZ type AATD) produce disease. Most patients with liver disease due to AATD are homozygous for the Z allele (ie, PI*ZZ); liver disease does not occur in null homozygotes who have severe deficiency of AAT, but no intra-hepatocytic accumulation.

**Keywords:** Alpha 1-antitrypsin deficiency, Liver cirrhosis, Protein C, protein S, Pulmonary embolism, DVT.

## Case Report

62-year-old, non-smoking, white Man with past medical history of AATD associated with emphysema but no other comorbidities present to the office with lower extremity swelling for 1 month. On physical exam he had 2+ pitting edema in lower extremities. Lung examination had fine rales bilateral bases. Patient was not short of breath it looks comfortable saturation was 99% room air. Vitals were stable. Considering lower extremity edema and history of AATD med me to think to check his liver functions he could have hypoalbuminemia and cirrhosis. Ultrasound of the liver demonstrated patient having cirrhosis and blood test revealed hypoalbuminemia that prompted he should be checked for D-dimers as probability was high. D-dimers were elevated subsequently went for ultrasound of lower extremity and DVT was found and subsequently CT scan showed pulmonary embolism, further workup showed decreased protein C and S. That typically due to decreased synthetic function of the liver cirrhosis due to AATD. Patient was admitted to the hospital started on heparin and got discharged within 24 hours to home with Newer oral anticoagulant Eliquis. Patient's other anticoagulation profile anti-thrombin III of 33 µ/dl (normal 85-130 µ/dl) with negative factor V mutation, lupus anticoagulant negative

### Workup

Laboratory diagnostics revealed white cell count of 71000 without any neutrophilia. D-dimers were elevated 2.0 8.

| | | |
|---|---|---|
| Sodium | Latest Ref Range: 136 - 145 meq/L | 139 |
| Potassium | Latest Ref Range: 3.5 - 5.1 meq/L | 4.1 |
| Chloride | Latest Ref Range: 98 - 107 meq/L | 104 |
| CO2 | Latest Ref Range: 21.0 - 31.0 meq/L | 29.7 |
| Anion Gap | Latest Ref Range: 7 - 17 meq/L | 5 (L) |
| BUN | Latest Ref Range: 7 - 25 mg/dL | 12 |
| Creatinine | Latest Ref Range: 0.60 - 1.30 mg/dL | 0.76 |
| eGFR (MDRD) | Unknown | 104.27 |
| Glucose | Latest Ref Range: 70 - 99 mg/dL | 78 |
| Calcium | Latest Ref Range: 8.6 - 10.3 mg/dL | 8.8 |
| Alk Phos | Latest Ref Range: 34 - 104 IU/L | 147 (H) |
| ALBUMIN | Latest Ref Range: 3.5 - 5.7 g/dL | 2.5 (L) |
| Total Protein | Latest Ref Range: 6.4 - 8.9 g/dL | 5.7 (L) |
| AST | Latest Ref Range: 13 - 39 IU/L | 49 (H) |
| ALT | Latest Ref Range: 7 - 52 IU/L | 39 |
| Total Bilirubin | Latest Ref Range: 0.3 - 1.0 mg/dL | 4.3 (H) |

Protein S activity 65% normal ranges 77 to 143%
Protein C activity 42% with range of 70 to 130%

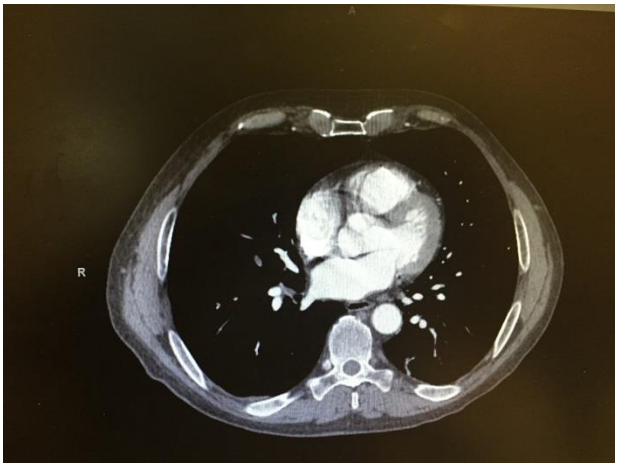

**Figure 1:** CT scan showing bilateral pulmonary embolism with mild right heart strain.

Lower extremity Doppler: Evidence of DVT involving the left calf muscle branches/gastrocnemius. No evidence of other DVTs or superficial phlebitis involving bilateral lower extremity.

CT scan chest stat done showed: Acute pulmonary emboli in both upper and lower lobes pulmonary arterial branches with mild right heart strain.

## Discussion

Although Alpha-1 Antitrypsin Deficiency (AATD) is generally considered to be rare, estimates that 80,000 to 100,000 individuals in the United States have severe deficiency of AAT suggest that the disease is under-recognized [1,2]. The prevalence of AAT varies considerably from one country to another [3]; however, it is estimated that more than 3 million people worldwide have allele combinations associated with severe deficiency of AAT [4,5].

AAT is a protease inhibitor (Pi) of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin. It is part of a larger family of structurally unique serine protease inhibitors, referred to as serpins, which have also been implicated in the pathogenesis of neurodegenerative diseases, angioedema, and coagulation abnormalities, collectively called "serpinopathies" [9,10].

Emphysema in AAT deficiency (AATD) is thought to result from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin. This mechanism is called a "toxic loss of function." Specifically, cigarette smoking and infection increase the elastase burden in the lung, thus increasing lung degradation [10]. In addition, the polymers of "Z" antitrypsin are chemotactic for neutrophils, which may contribute to local inflammation and tissue destruction in the lung [11].

The pathogenesis of the liver disease is quite different and is called a "toxic gain of function." The liver disease results from the accumulation within the hepatocyte of unsecreted variant AAT protein. Only those genotypes associated with pathologic polymerization of AAT within the endoplasmic reticulum of hepatocytes (eg, PI*ZZ type AATD) produce disease [6-8]. Most patients with liver disease due to AATD are homozygous for the Z allele (ie, PI*ZZ); liver disease does not occur in null homozygotes who have severe deficiency of AAT, but no intra-hepatocytic accumulation. Patient did not have any other significant meds will history that can lead to hypercoagulability except alpha 1 antitrypsin deficiency leading to liver cirrhosis causing decreased protein C and S activity leading to DVT and pulmonary embolism.

We are publishing the unique AATD with hypoalbuminemia and decreased protein C and S activity leading to pulmonary thrombosis. This case is important and sheds light in primary care office is the patient with AATD presents for lower extremity swelling should be worked up for hypoalbuminemia leading to protein C and S deficiency and ultimately leading to pulmonary embolism.

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