

Alpha-1-Antitrypsin Deficiency Initially Presenting in an Adult Surgical Patient: A Case Report and Review of Current Understanding of Disease Process

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Citation

S Haque, N Pope, N Azumi. *Alpha-1-Antitrypsin Deficiency Initially Presenting in an Adult Surgical Patient: A Case Report and Review of Current Understanding of Disease Process*. The Internet Journal of Pathology. 2009 Volume 10 Number 2.

Abstract

Alpha-1-antitrypsin (AAT) is one of several serpin molecules which functions to balance the action of various endogenous proteolytic enzymes. A deficiency of functional levels of this enzyme is most commonly inherited in an autosomal recessive fashion. Greater than 95% of AAT-deficient persons are homozygous for the non-functional Z-variant of the enzyme. ZZ-homozygosity is relatively common, affecting 1 in 2500 persons of northern European decent. Known complications of AAT-deficiency include early-onset emphysema, childhood liver disease, cirrhosis, and increased incidence of hepatocellular carcinoma¹. Although AAT-deficiency is frequently diagnosed in early childhood, it is not uncommon for persons to go undiagnosed for many years until otherwise unexplained lung or liver disease become evident. We report a case of AAT-deficiency in a 44-year-old female which became evident post-operatively after unexplained, uncontrollable ascites and respiratory failure.

INTRODUCTION

Alpha-1-antitrypsin (AAT) is produced primarily in hepatocytes and functions to counteract neutrophil elastase and various other proteolytic enzymes in the lung. The discovery of early emphysematous changes in young, non-smoking individuals and subsequent elucidation of the disease process served as the foundation of the protease-protease-inhibitor theory of chronic lung disease. The normal M-variant of the AAT protein is encoded for on chromosome 14q and undergoes post-translational modification within the endoplasmic reticulum (ER) of hepatocytes before being released into the serum. The functional molecule consists of a mobile reactive center loop and a β -pleated sheet. These sites serve as a decoy substrate for protease binding. After cleavage by the protease, AAT undergoes a conformational change which disrupts the catalytic site of the protease, thus rendering it inactive^{2,3,4,5}.

The most common manifestation of AAT-deficiency occurs in individuals homozygous for the Z-variant of the AAT gene. This mutation causes a single amino acid substitution which alters the secondary and tertiary structure of the normal β -pleated sheet-reactive center interaction. The Z form of AAT allows for insertion of the reactive loop of one molecule into the β -sheet of another. This process may be

repeated ad infinitum resulting in large polymers of Z-AAT. These polymers are too large to be transported out of the ER and result in intracytoplasmic, PAS-positive inclusions which are classically seen in the hepatocytes of AAT-deficient patients⁶. In addition to being largely secluded and subsequently degraded within hepatocytes, Z-AAT protein which does reach the serum has approximately half the functionality of the wild-type M-AAT⁷. Approximately 85% of the Z-AAT produced in homozygous individuals remains within the ER of hepatocytes⁸. The exact mechanism by which these polymer-inclusions cause liver dysfunction is not well understood.

Liver dysfunction in AAT-deficiency frequently becomes evident early in life and may present as persistently elevated bilirubin and transaminase levels. Of these AAT-deficient neonates with evidence of liver injury, population-based studies show that 80% will show only mild evidence of hepatic disease which typically resolves in late adolescence. The remaining 20% will experience more severe liver disease and many patients from this cohort require early liver transplantation⁹. Still, other patients will show virtually normal liver function throughout childhood and develop liver injury later in life. What eventually tips the balance and causes manifestations of liver disease in these patients

remains largely undiscovered, although various environmental factors and physiologic stressors have been implicated^{10, 12-16}.

CASE REPORT

The patient was a 44-year-old female with a past medical history significant for gastric bypass complicated by the development of volvulus and subsequent necrotic bowel leading to small bowel resection 3 months prior to admission. She had also experienced a saddle pulmonary embolism 2 months prior to this admission complicated by a retroperitoneal bleed on anti-coagulative therapy which led to the placement of an IVC filter. She had no other known history of pulmonary or hepatic dysfunction. The patient was transferred from an outside hospital to our institution with 1-2 weeks of increasing abdominal girth, abdominal pain, and recurrent ascites which was negative for malignancy. Cultures done at an outside hospital eventually grew both fungal and gram-positive microbes. The patient was placed on broad-spectrum antibiotics with enteric coverage and discharged home following a seven day course. Several days after her previous hospital stay, she presented to our institution with acute shortness of breath and recurrent ascites. Her shortness of breath progressed and ultimately required intubation and admission to the medical ICU. The surgical service followed her during her hospital stay given her recent abdominal surgeries. Suspicion of small bowel obstruction was raised after an abdominal CT showed high-grade narrowing of the small bowel. Her ascites persisted despite frequent draining, and repeated CT scans showed no change from the previously mentioned study. Her liver function tests on admission were as follows: total protein 4.6, albumin 1.6, direct bilirubin 0.3, SGOT 24, SGPT 15. Between paracenteses, she repeatedly required higher pressures to adequately maintain ventilation. She developed a leukocytosis and was intermittently febrile. It was felt that her respiratory dysfunction was largely due to diaphragmatic compression secondary to her massive ascites. Due to the previous CT images and a lack of other explanation for her massive, recurrent ascites, she was taken to the OR for exploratory laparotomy. During this procedure, a large amount of straw-colored fluid was drained and inspection of the bowel revealed multiple loops extensively adherent to one another which were unable to be separated safely. There was no evidence of ischemic or perforated bowel. The peritoneum was extensively lavaged and drains were placed in the pelvis and pericolic gutters. Post-operatively the patient was able to be extubated; however, she required re-

intubation 24 hours later due to marked tachypnea. She would eventually develop a ventilator-associated pneumonia which was proven to be *Pseudomonas* by bronchoalveolar lavage. Despite the addition of intraperitoneal Amikacin, and the placement of bilateral pigtail abdominal drains, the patient's leukocytosis persisted and she continued to require vasopressors to maintain adequate blood pressures. She eventually succumbed to her multiple medical conditions.

On post-mortem examination, her liver weighed 3000 gm and demonstrated significant hepatomegaly with extensive centrilobular necrosis without evidence of cirrhosis or fibrosis. On microscopic examination, hepatocytes demonstrated numerous, classic round eosinophilic cytoplasmic inclusions (Figure 1) which were proven to be AAT accumulations by immunohistochemistry (Figure 2). Her spleen was also enlarged and congested.

Figure 1

Figure 1- Hepatocytes showing round intracytoplasmic acidophilic inclusions.

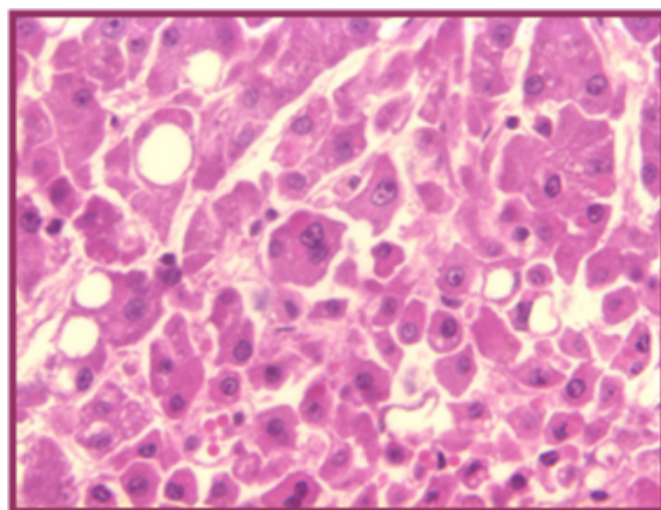
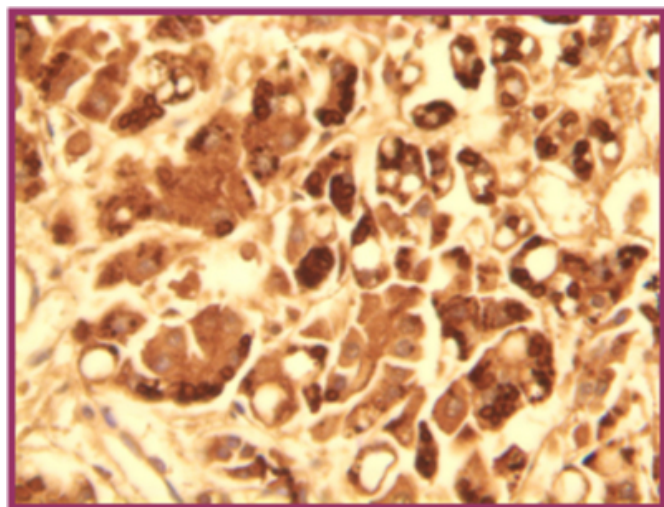


Figure 2

Figure 2- Immunohistochemical stain for AAT.



The patient's lungs were congested with extensive emphysematous changes and intra-alveolar hemorrhage (Figure 3). Acute bronchopneumonia was also appreciated which later grew *Pseudomonas* (Figure 4).

Figure 3

Figure 3- Lungs displaying severe intra-alveolar hemorrhage.

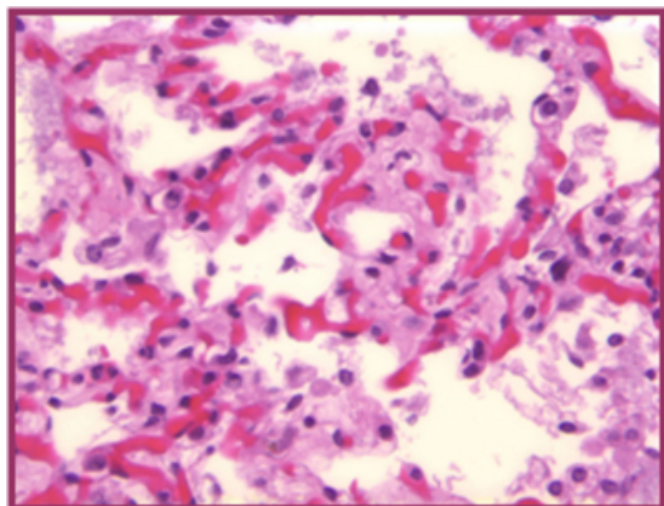
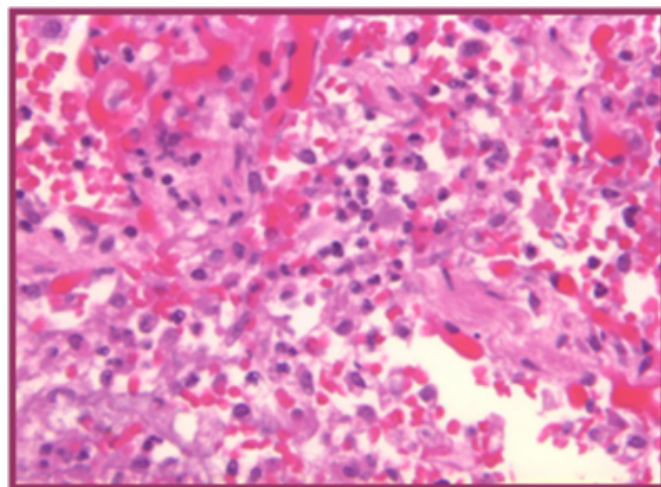


Figure 4

Figure 4- Acute bronchopneumonia.



DISCUSSION

Alpha 1-Antitrypsin deficiency is the most common and most clinically significant of the serpinopathies. The altered structure of a single protein results in both damage related to the absence of the normally functional protein, as well as from the accumulation of the abnormal entity. This disorder classically manifests in childhood as hepatic dysfunction. The diagnosis is typically confirmed by one of three methods; a serum test revealing low functional levels of AAT, protein phenotyping by isoelectric focusing or most commonly by genotyping for common AAT-mutations¹¹.

The pulmonary manifestations of AAT-deficiency have been well characterized, the hallmark of which is the early onset of panacinar emphysema secondary to the loss of activity of the native antitrypsin protein in counteracting the deleterious effects of several native proteases. The development and progression of these emphysematous changes are exacerbated by smoking. The logical and current therapy for such a deficiency is proteinase-inhibitor replacement therapy. Results of replacement therapy have been mixed, with patients frequently continuing to experience further pulmonary destruction despite smoking cessation and adequate enzyme replacement therapy¹². In addition, Mahadeva et al¹³ reported that the 10-15% of mutant AAT which makes it into the plasma frequently adheres to the alveolar wall, polymerizes and serves as a direct chemoattractant for neutrophils. This may account for the increased neutrophilic infiltrate typical in ZZ-AAT lungs, and likely augments the damage done by unopposed neutrophilic enzymes.

In any patient with limited pulmonary reserve, ventilator-associated pneumonia represents a significant threat to life. *Pseudomonas pneumonia* is notoriously difficult to treat, and frequently manifests as a multi-drug resistant pneumonia and is more common in patients with COPD¹⁴. Our patient also suffered from a multi-drug resistant *Pseudomonas pneumonia*.

It is difficult to accurately attribute how much of the respiratory failure our patient experienced was attributable to her pre-existing and previously unknown lung pathology. Certainly, the decrease in her pulmonary reserve coupled with a difficult pneumonia complicated by the mechanical difficulties associated with her increased intra-abdominal pressure created a situation from which recovery was difficult if not unattainable.

In addition to her pulmonary complications, our patient suffered from significant liver pathology. In contrast to the fairly detailed level of understanding we have regarding lung pathology resulting from AAT-deficiency, much of what we understand of the hepatic aspect of the disease remains theoretical. In neonates, hepatitis and cholestatic jaundice may appear in 20% of newborns. Ghishan et al reported a case of a 2-week-old baby who presented with cirrhosis and ascites secondary to AAT-deficiency of Pizz phenotype¹⁵. While the disease may cause hepatitis or cirrhosis in the neonatal period, it remains silent in adults until mid- to late life, when patients first present with signs of liver failure. In fact, the only distinctive feature of hepatic disease in adults may be the presence of PAS-positive diastase resistant acidophilic cytoplasmic globules in the hepatocytes. However, even a minor abdominal or liver insult such as gallstone ileus or bowel ischemia is speculated to precipitate a rapidly progressive liver disease or fulminant failure¹⁹.

There is great variability in clinical presentation of adult patients with AAT-deficiency. Stauber et al presented a 63-year-old man with severe AAT-deficiency of proteinase inhibitor Z, emphysema, cirrhosis, mesangioproliferative glomerulonephritis, and nephrotic syndrome¹⁶. AAT-deficiency should be considered in the differential of patients with concomitant liver and kidney dysfunction¹⁶. Korver et al described a case of a 60-year-old man who had panniculitis with ulcerating plaques on chest, abdomen, and lower extremity that did not resolve with antibiotics or steroids¹⁷. Work up revealed that the patient had emphysema and AAT-deficiency of PiZZ phenotype. Similar study was conducted in three Swedish hospitals, revealing incidental

discovery of severe AAT-deficiency of either PiSZ or PiFZ phenotype in eight patients with systemic necrotizing vasculitides¹⁸. Some adults may present with only intractable ascites¹⁹. Considering the degree of variability in clinical presentation of AAT-deficiency, awareness of such is key in early diagnosis and treatment.

On the molecular level, several theories have been proposed regarding the hepatic aspect of the disease. One theory proposed by Teckman and Perlmutter explaining the hepatic damage which occurs in Z-AAT individuals revolves around the autophagic response seen in these diseased hepatocytes¹⁹. The autophagic response normally functions to sequester and destroy non-functional organelles within the cytoplasm of many types of cells. These autosomes then fuse with lysosomes to form the autolysosome, where degradation of non-functional organelles occurs. The constant polymerization of Z-AAT within the hepatocytic ER is thought to cause a constitutively activated autophagus response. During times of physiologic stress, these cells would have little reserve to increase their autophagus response and clear cellular debris in order to preserve cellular function. Teckman et al have subsequently demonstrated that the physiologic stress of fasting in ZZ-AAT mice resulted in an increase in hepatic steatosis, and no increase in autophagus activity above their constitutively high baseline²⁰. Such physiologic stress may overwhelm the ability of the highly activated autophagous system to maintain an adequate cellular environment, thereby leading to cell death. This may also explain the increased incidence of hepatocellular carcinoma in ZZ-AAT patients, as autophagic activity has been shown to decrease tumorigenesis in rats²¹. The observation of increased hepatic fat deposition is also consistent with the steatosis seen in our patient at post-mortem examination.

In addition, Permuttler has investigated the role of mitochondrial damage in ZZ-AAT hepatocytes²². The observation that ZZ-AAT deficient patients who suffer from significant liver disease frequently have large numbers of mitochondria within autolysosomes implies that mitochondrial damage may have a role in hepatic pathogenesis. While the mechanism of this damage remains unclear, two theories have been proposed. The presence of ZZ-AAT polymers within the ER may trigger mitochondrial damage directly, as signaling between these two organelles has previously been established²³. Mitochondrial damage may also be induced by the constant autophagous response

known to exist within these cells.

An additional environmental factor which has been theorized to trigger hepatocellular damage in ZZ-AAT individuals is increased temperature as may be seen during acute febrile episodes. Although studies have indicated that increased temperature does increase the polymerization of the mutant Z-AAT molecules in vitro²⁴, An et al have demonstrated that fever-range temperatures do not have any effect on the steady-state levels of Z-AAT polymer in an in vivo mouse system²⁵. An interesting point raised by the authors of this study is that because AAT normally functions as an acute phase reactant, the febrile-range body temperature in their study were induced by the application of external heat, thus still allowing for the possibility that Z-AAT polymerization may be induced by the systemic inflammatory response rather than the associated increased body temperature.

Which initial stressor precipitated the liver dysfunction in our patient is difficult to pinpoint. While several of the above known stressors were present in the months leading up to our patient's presentation, no one may have acted alone; rather, a combination of these factors may have stressed an already damaged liver.

CONCLUSION

Alpha-1-antitrypsin deficiency represents an uncommon but important source of pulmonary and hepatic disease. While diagnosis of this condition is frequently made in the pediatric population, AAT-deficiency may initially present in the adult patient with otherwise unexplained hepatic or pulmonary dysfunction. Here, we have presented the initial presentation of AAT-deficiency in an adult patient in the context of intra-abdominal pathology. This remains a rare but important diagnosis which requires a high degree of suspicion, particularly in patients with concomitant hepatic and pulmonary disease.

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