The Application of Clinical Genetics

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CASE SERIES

Vascular Pathology in Alpha 1 Antitrypsin Deficient Chronic Obstructive Pulmonary Disease and Emphysema Patients: Case Reports

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Abstract: Alpha 1 Antitrypsin Deficiency (AATD) is a genetic condition that results from mutations in the *SERPINA1* gene, which can lead to deficient or dysfunctional Alpha 1 Antitrypsin (AAT) protein production. AATD is linked to chronic obstructive pulmonary disease (COPD) and emphysema. In addition to pulmonary manifestations, AATD has also been associated with vascular pathology due to excessive protease activity, tissue degradation, and vessel stiffening. Early AATD diagnosis is crucial to prevent progressive lung damage and associated pathologies. Here, we present case reports of two patients with AATD from the Temple University Hospital Outpatient Clinic, who exhibited aneurysms of the aorta and splenic artery. AATD should be considered a genetic risk factor for aneurysms and vascular diseases, necessitating cardiovascular monitoring in affected individuals. This report emphasizes both the need for heightened awareness of AATD as a potential etiology of unexplained vascular aneurysms, as well as the need for screening for vascular pathology in patients with AATD-associated COPD and emphysema to facilitate early intervention and improve patient outcomes.

Keywords: alpha 1 antitrypsin, lung disease, aneurysm, aneurysm disease, vascular pathology, vascular disease

Introduction

Alpha 1 Antitrypsin Deficiency (AATD) was first recognized as a genetic condition associated with early-onset chronic obstructive pulmonary disease (COPD) and emphysema in 1963.[1] It is characterized by the expression of defective Alpha 1 Antitrypsin (AAT) proteins with reduced functionality, and/or the absence/reduction of serum AAT levels, caused by mutations in the *SERPINA1* gene.[2] In healthy individuals, AAT inhibits neutrophil elastase activity within lung tissue; in patients with AATD, deficient or dysfunctional AAT levels lead to uncontrolled neutrophil elastase action, resulting in degradation of elastin in the lung. Consequently, this causes damage and loss of elasticity, and can lead to the development of COPD and emphysema.[3] However, recent research has shown that, contrary to the expected, patients with COPD can exhibit with increased serum AAT levels. A study on the biochemical alterations in serum AAT levels in patients with COPD showed that mean serum AAT levels were significantly higher in those with COPD compared to individuals with normal lung function, suggesting that COPD may be responsible for increased AAT levels in some patients.[4]

Individuals with AATD who are homozygous for the mutant Z allele of *SERPINA1* (proteinase inhibitor [PI]*ZZ) typically have severe AATD, with serum AAT levels below 10 µM (<52 mg/dL), compared to 17–47 µM (102–254 mg/dL) seen in healthy individuals who are homozygous for the normal M allele (PI*MM).[5] It is estimated that the PI*ZZ and PI*SZ genotypes affect approximately 1.5 million people worldwide,[6] and 120,000 people in Europe have the PI*ZZ genotype.[7]

Received: 5 September 2024
Accepted: 8 January 2025
Published: 28 January 2025

However, AATD is a largely underdiagnosed condition and it has been estimated that only 15–30% of cases have been diagnosed in European countries.[8]

As AATD diagnosis rates are improving, it has become increasingly evident that other systems are also implicated in AATD pathogenesis. The action of AAT is not limited to lung function, as AAT is a systemic protein, with various anti-inflammatory and immunomodulatory properties.[3] Furthermore, patients with AATD often experience additional extrapulmonary manifestations that are associated with the Z allele, such as liver disease, panniculitis, and vasculitis.[3] Reports have also linked AATD to vascular pathology, including aortic aneurysm disease with dissection, and increased cardiovascular risk.[3,9] Evidence suggests that deficiency of functional AAT contributes to a range of cardiovascular diseases, resulting from the protease-antiprotease imbalance that is associated with AATD.[10,11] Here, we report two patients with AATD from Temple University Hospital who, in addition to COPD and emphysema, exhibited vascular pathology likely related to AATD.

Case Presentation

In the outpatient clinic at the Temple University Hospital in Philadelphia, patients with a history of COPD and emphysema and previously exhibited aneurysms were identified, specifically with aneurysms in the aorta and splenic artery. At the time of selection, patients were receiving treatment for COPD and emphysema at the Temple University Hospital.

Case 1

A 70-year-old White female, who received a diagnosis of AATD (PI*ZZ) at the age of 65. Additional diagnoses included chronic lymphocytic leukemia since the age of 64 (currently untreated), triple-negative breast cancer diagnosed at the age of 67 (treated with chemotherapy and mastectomy), and Raynaud's disease. The patient has reported shortness of breath with exercise, which has progressively worsened since the age of 40; however, no supplemental oxygen was prescribed, and the patient has never smoked. At the age of 65, the patient was admitted to hospital due to pain in the left upper abdomen. Subsequent computed tomography (CT) abdominal angiogram with contrast lead to the diagnosis of a ruptured aneurysm of the splenic artery (Figure 1).

The spleen was not removed but the aneurysm was successfully treated by coiling to stop the bleeding. The diagnosis of AATD was made three months after this event, when the patient consulted a pulmonologist for increased shortness of breath; AAT augmentation therapy for AATD then commenced. Several subsequent high-resolution CT scans showed extensive panlobular emphysema and bronchiectasis, primarily in the lower lobes, and during a more recent CT scan in the last year, the

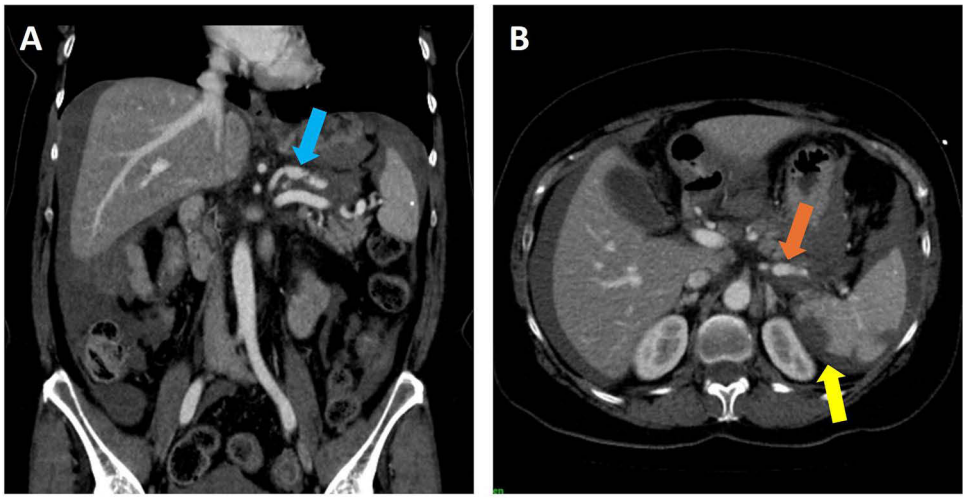

Figure 1 (**A**) Coronal reconstructed image of abdominal angiogram via CT with intravenous contrast showing irregular aneurysmal dilatation of splenic artery (blue arrow). Evidence of rupture is seen with hemorrhage in the left subdiaphragmatic and perisplenic regions. (**B**) Axial image of contrast-enhanced abdominal CT, which demonstrates splenic artery aneurysm (orange arrow). There are splenic infarcts seen secondary to arterial rupture with hemorrhage in the left upper abdomen (yellow arrow).
Abbreviation: CT, computed tomography.

ascending aorta was dilated to 41 mm. The most recent pulmonary function tests reveal a forced vital capacity (FVC) of 2.44 L, a forced expiratory volume in 1 second (FEV_1) of 1.55 L pre-bronchodilation, and 1.58 L post-bronchodilation, which places the patient within stage 2 of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. An FEV_1/FVC ratio of 63.6% pre-bronchodilation and 64.2% post-bronchodilation was also recorded. Total lung capacity (TLC) was 124% of predicted and residual volume (RV) post-bronchodilator was 3.50 L (170% of predicted); diffusion capacity was 58% of predicted.

The patient's family history revealed one sister who was also diagnosed with AATD, and has COPD and emphysema; the sister is currently receiving AAT augmentation therapy. Her diagnosis was established after the index case had been diagnosed with AATD. The father (who had unspecified heart disease) and paternal grandmother were known to have died from cerebrovascular accidents; they had not been tested for AATD and it is not known whether they also had COPD.

Case 2

A 52-year-old White male, who received a diagnosis of COPD at the age of 36 and a diagnosis of AATD (PI*ZZ) at the age of 46. At the age of 49, the patient's pulmonary function tests showed a post-bronchodilator FEV_1 of 3.85 L (52% of predicted normal, decreased from 60% of predicted 2 years prior), which places the patient within stage 2 of the GOLD classification. He also had a FVC of 4.88 L (104% of predicted normal) and a FEV_1/FVC of 39.4%. The patient displayed hyperinflation (121% of predicted normal), with a RV of 2.79 L (143% of predicted), and had a reduced diffusion capacity of 11.2 mL/mmHg/min (31% of predicted normal). Other issues included hypertension, obesity (class 2; 36.3 kg/m^2), and moderate obstructive sleep apnea. Before quitting in 2017, the patient had a history of smoking (approximately 28 pack years).

At age 46, he experienced severe substernal chest pain that prompted the patient to seek emergency room (ER) treatment. However, the pain was believed to be costochondritis precipitated by cough and symptomatic pain control was provided. Two months later, he visited the ER again due to similar chest pain, which was more severe than the previous. Further diagnostic tests and a CT angiogram of the chest revealed a type B aortic dissection. Initial blood pressure was 200/110 mmHg, which was treated aggressively and normalized to 120/110 mmHg. The CT angiogram (aorta protocol) showed the aortic dissection with a large false lumen that had collapsed into the true lumen of the aorta, extending from the left subclavian artery to the right iliac artery. The iliac arteries and all major visceral vessels were connected to the true lumen. An endovascular stent was placed, reaching from the left subclavian artery to the celiac artery in the abdomen. During the stenting procedure, the dissection was seen approximately 1 cm below the origin of the left subclavian artery, at the entry site. The patient recovered well from the procedure and his blood pressure and respiratory status remained stable with conventional therapy for COPD and emphysema. It is of interest to note that AATD (PI*ZZ) was diagnosed at the time of this admission, and initiation of AAT augmentation therapy also took place at this time.

Current treatment includes bronchodilator therapy and steroids when indicated, as well as weekly AAT augmentation therapy. His hypertension is treated intermittently. The most recent CT angiogram shows a stable aortic aneurysm (Figure 2).

The patient has two siblings who are heterozygous for the Z allele (PI*MZ); both are healthy and do not have physical limitations. His father, who had never been tested for AATD, died suddenly at the age of 56. The cause of death was assumed to be a myocardial infarction due to severe coronary artery disease; however, no autopsy was carried out to confirm.

Discussion

The two patients described have a history of COPD and emphysema, a diagnosis of AATD, and vascular pathology. Their experiences exemplify other reports of patients with AATD and aortic dissection and vascular aneurysms.[5,9,12,13] In a previous study, significantly reduced AAT levels in aortic wall specimens of aneurysms and acute dissections when compared to healthy aortic walls have been reported,[14] indicating that a deficiency in AAT in the aortic wall may increase susceptibility to dissection. AAT has demonstrated a protective role in preserving arterial wall integrity, as well as regulation of inflammatory processes underlying cardiac events.[10] The lack of functional AAT in patients with AATD results in uninhibited activity of endogenous proteases breaking down elastin and connective tissues, leading to a loss of elasticity, increased stiffness, and reduced distensibility of blood vessels.[5,9,11,12,15,16] It has also been reported that a small number of patients with Raynaud's disease, as seen in Case 1, present with lower levels of serum AAT when compared

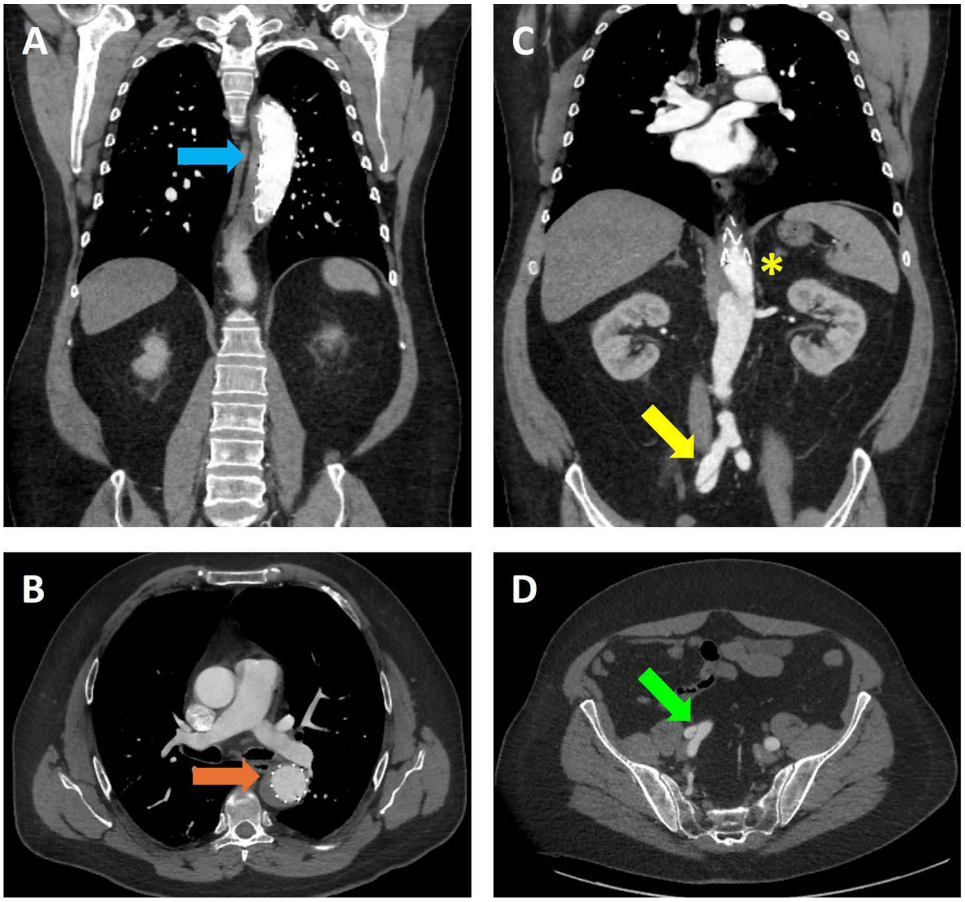

Figure 2 (**A**) Coronal reconstructed image of angiogram via CT with intravenous contrast showing type B descending aortic aneurysm arising from the left subclavian artery. Endovascular stenting is visualized with thrombosis of the false lumen in the thoracic region (blue arrow). (**B**) Axial image of contrast-enhanced CT, again demonstrating the presence of an endovascular stent and partial thrombosis of the false lumen (orange arrow). (**C**) Coronal reconstructed image of angiogram via CT with intravenous contrast demonstrating both termination of the endovascular stent at the level of the diaphragmatic hiatus (yellow asterisk) and the presence of a false lumen that extends down to the right iliac artery (yellow arrow). (**D**) Axial image of contrast-enhanced CT, again demonstrating extension of the false lumen to the right iliac artery (green arrow).
Abbreviation: CT, computed tomography.

with healthy controls.[17] It is therefore plausible that the uninhibited action of proteases in cases of AATD should also affect other tissues besides the alveoli, and hence, it is justifiable to regard AATD as a genetic risk factor for vascular aneurysms and aortic dissection. For this reason, we advise cardiovascular monitoring for patients diagnosed with AATD.

Changes to the elasticity of the aortic wall are associated with increased risk to aneurysm disease, which is seen in other pathogenic conditions that affect connective tissue, such as Marfan syndrome and Ehlers–Danlos syndrome.[18] Therefore, it is possible that in the described patient cases, their deficiency in serum AAT levels contributed to the development of their vascular pathology. The patient in Case 1 exhibited a large aortic diameter, which is consistent with evidence demonstrating that the diameter of the ascending aorta is larger in patients with AATD and emphysema.[9,16,19] Previously, Dako et al[9] reported a significant positive correlation between ascending aortic diameter and age in patients with AATD. An increase in aortic diameter can be considered a precursor to aneurysm development; thus, it is reasonable to recommend monitoring the aortic diameter of patients who have been diagnosed with AATD. Although the patient in Case 2 suffered a dissection of the descending aorta on the basis of a distended descending aorta and a hypertensive crisis, the ascending aorta was not enlarged. Although dissection can occur without a pre-existing aneurysm,[15,20] the presence of an aneurysm is a major precursor for dissection.

Aortic aneurysms can be referred to as "silent killers" since they are often asymptomatic before rupture. However, there are several symptoms that can lead to an aneurysm diagnosis.[21] Abdominal aneurysms can be suspected when a pulsating abdominal mass is found, or with more subtle signs that have also been previously reported.[21,22] In both

Cases 1 and 2, the patients experienced substernal chest pain and atypical abdominal pain that led to the aneurysm diagnosis, and the subsequent successful life-saving treatment using coiling and stenting.

The American Thoracic Society and other medical organizations recommend screening patients with COPD and emphysema for AATD;[2,23] however, AATD is still substantially underdiagnosed, mostly due to insufficient testing.[8,24] In the presented cases, despite the patients' long history of COPD, they were not initially tested for AATD and were only tested/diagnosed with AATD following the ruptured splenic arterial aneurysm and aortic dissection (Case 1 and Case 2, respectively). Early diagnosis of AATD is essential to prevent progressive damage to the lungs and to prevent other pathologies that are associated with the condition. It has been noted that physicians treating patients with emphysema often observe a distended ascending aorta, which can be easily seen and measured on chest CT scans. In addition, vascular surgeons who treat patients with aortic aneurysms have frequently noticed the presence of emphysema due to the challenge associated with general anesthesia (ventilation in particular; Paul J. DiMuzio, MD, Jefferson Hospital, personal communication, 2020). Therefore, it would seem reasonable to expand the scope of research in COPD and emphysema to include vascular pathology.

Screening techniques such as CT angiography can be employed for aortic aneurysm detection and duplex ultrasonography can be used for identifying visceral aneurysms.[25] CT abdominal angiogram can reveal aneurysms of the splenic artery aneurysm (as demonstrated with Case 1; Figure 1), which is a phenomenon that has been described previously as a complication of cirrhosis and portal hypertension.[25] Gaglio et al[25] identified 21 cases of splenic artery aneurysm collected from over 30 liver transplant centers, 10 of which were associated with AATD (particularly the Z allele); furthermore, AATD was the most common cause of cirrhosis in around 40% of cases. In those cases, portal hypertension and the subsequent increase of splenic artery pressure, in addition to arterial wall damage due to increased protease activity, could explain aneurysm formation and rupture.[25,26] However, the patient in Case 1 had no evidence of liver disease or portal hypertension, suggesting that AATD alone was the predisposing contributor to aneurysm development and rupture. Other reports exist of aneurysms that can occur at other sites in individuals with AATD. For instance, Jaruvongvanich et al[27] reported a case of a patient with a ruptured gastric artery aneurysm as a complication of AATD, along with moderate dilation of the splenic artery and portions of the distal renal arteries. While additional data is needed to draw definitive conclusions, it is plausible that AATD may predispose individuals to aneurysm formation at various specific anatomical sites, including the mesenteric and cerebral arteries.[27–31] The emergence of aneurysms at different anatomical locations among AATD patients suggests a need for comprehensive monitoring of patients, as well as further research, to elucidate the full spectrum of potential sites for aneurysm formation in this population.

It has also been reported that specific AATD genotypes are associated with aneurysms in different locations of the aorta.[9,12] Dako et al[9] reports that ascending aortic aneurysms are associated with the homozygous PI*ZZ genotype, whereas abdominal aortic aneurysms are associated with heterozygous AATD genotypes.[12] Individuals who are heterozygous for the Z allele (ie PI*MZ) have a more favorable protease-antiprotease balance than PI*ZZ individuals; however, the deficiency of functional AAT in PI*MZ individuals can still result in overactivity of neutrophil elastase, leading to increased inflammation.[32] While data is limited, there are studies that describe an association between heterozygous AATD genotypes, such as PI*MZ, and increased cardiovascular risk and abdominal aneurysm development.[33,34] In both cases described here, there is a family history of the *SERPINA1* Z allele and cardiovascular disease, suggesting that the presence of the Z allele may predispose individuals to the increased risk of cardiovascular disease, further supporting the consideration of AATD as a genetic risk factor.

Conclusion

The patients described herein experienced serious vascular events that could be associated with AATD. Early AATD diagnosis prior to catastrophic events is vital to prevent damage to the lungs and development of other pathologies. The lack of functional AAT in patients with AATD results in uninhibited action of endogenous proteases in the lung and may also lead to increased stiffness and reduced distensibility of blood vessels, increasing the risk of developing aneurysms and dissection. We propose that AATD could be a genetic risk factor for aneurysms and vascular disease, which warrants regular monitoring of AATD patients for cardiovascular involvement.

Informed Consent

Institutional Review Board approval was sought but not deemed applicable. Patients verbally provided their informed consent to the Corresponding Author for their clinical and laboratory information to be published. This consent was witnessed and documented accordingly.

Acknowledgments

Secretarial work was provided by Angelina Smith-Robinson and Tina Ritter. Medical writing assistance was provided by Alice Hudson from Bioscript Group, Macclesfield, UK, in accordance with Good Publication Practice Guidelines, funded by CSL Behring.

Funding

This research did not receive any specific grants for funding.

Disclosure

MG, ELS, MK, and FK declare no competing interests in preparing this article. AJG reports reimbursement and support for attending meetings and/or travel from Temple Lung Center, Philadelphia and received grants from Patient-Centered Outcomes Research Institute (PCORI), University of Illinois at Chicago, Department of Defense Congressionally Directed Medical Research Program (CDMRP) and National Institute of Health. He also reports small percentage of effort supports to institution from Video Telehealth Pulmonary Rehabilitation to Reduce Hospital Readmission in Chronic Obstructive Pulmonary Disease (TeleCOPD), Roflumilast or azithromycin to prevent COPD exacerbations (RELIANCE) Study, and Cooling to Help Injured Lungs (CHILL Study), outside the submitted work.

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