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CASE REPORT

Fulminant hepatic failure in the setting of progressive ANCA-associated vasculitis associated with a rare alpha-1 antitrypsin phenotype, 'PiEE'

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SUMMARY

Abnormalities in alpha-1 antitrypsin (AAT) proteins are risk factors for human disease. While the most common is AAT deficiency, a genetic disorder associated with chronic obstructive pulmonary disease, additional disorders associated with AAT abnormalities are increasingly recognised. We describe a middle-aged woman who presented with fulminant hepatic and multiorgan failure. Evaluation revealed the patient to have a rare AAT phenotype PiEE. Her clinical presentation was consistent with antineutrophilic cytoplasmic antibody-associated vasculitis, and her history suggested features of panniculitis. This is the first description of this rare homozygous AAT phenotype and possible disease associations with the 'E' protein. Given that abnormal AAT are under-recognised, and that new mutations and phenotypes continue to be identified, we will need to expand on our knowledge base and report clinical manifestations associated with these abnormal phenotypes.

BACKGROUND

Abnormalities in the alpha-1 antitrypsin (AAT) protein are risk factors for human disease.[1] The most well described is AAT deficiency, a genetic disorder associated with chronic obstructive pulmonary disease (COPD) and liver injury.[1] Additional conditions such as vasculitis and panniculitis have been reported.[2] While classic AAT deficiency is diagnosed with low circulating levels of AAT, other rare mutations in the SERPINA1 gene can yield AAT proteins that are dysfunctional and predispose susceptible individuals to human disease despite normal circulating levels.[2] We describe a case of a woman presenting with fulminant multiorgan failure in setting of previously undiagnosed and progressive ANCA-associated vasculitis with a rare AAT phenotype of PiEE.

CASE PRESENTATION

A 48-year-old woman presented to our intensive care unit (ICU) with a 10-day history of myalgias, fatigue, anorexia and progressive dyspnoea. Her initial evaluation in the emergency department was notable for confusion and jaundice. Initial vital signs were notable for hypotension, tachycardia and hypoxaemia with room air saturation of 82%. Laboratory evaluation revealed profound metabolic derangements (see table 1) including elevated liver enzymes, acute kidney injury and a marked lactic acidosis (14 mmol/L) with a calculated anion gap of 43 mmol/L. Over the course of a few hours, her condition further deteriorated with cardiovascular collapse that required multiorgan support with mechanical ventilation and vasopressor dependence despite fluid resuscitation. Acute kidney injury progressed to anuric renal failure requiring renal replacement therapy. Inpatient work-up in the ICU included CT scan of the chest, abdomen and pelvis which demonstrated bilateral pulmonary consolidations with areas of cavitation (see figures 1 and 2), pancolitis to level of rectum and presence of free fluid in the abdomen.

The patient's medical history was notable for a recently suspected but poorly defined autoimmune process. Two years prior to her current presentation, she had been evaluated by otolaryngology for palatal abnormalities. She was diagnosed with an infected palatal polyp that had progressed over several years with development of a defect in her hard and soft palate and recurrent sinusitis. As a result, she had difficulty with oral intake and chronic tooth pain. She reported depression as a result of her medical issues and had begun to use cocaine and alcohol as a consequence. A screening rheumatological evaluation done for evaluation of the palatal defect by her primary care provider revealed a positive antinuclear antibody and a positive antineutrophilic cytoplasmic antibody (ANCA) titre of 1:640 with a perinuclear pattern (see table 2). She was referred to rheumatology for further evaluation.

Over a similar time frame, she noted recurrent rashes over her lower extremities with associated pain, erythema and oedema. She had six separate episodes of rash, erythema and pain by the time of her current admission. These episodes initially resolved with elevation of the affected body part and ice packs. With later recurrences, the rashes would continue to cause symptoms despite repeated antibiotic administration and overall she had a poor response to medical therapy. Given palatal abnormalities, positive ANCA and skin findings, she was referred to dermatology where she underwent punch biopsy. While negative for findings of vasculitis, the biopsy demonstrated dermal fibrosis with associated perivascular lymphohistiocytic inflammation and subcutaneous fat degeneration (figure 3).

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Table 1 Admission laboratory evaluations

Comprehensive	Latest reference range	Reported values
Sodium	133–144 mmol/L	125 (L)
Potassium	3.4–5.3 mmol/L	2.3 (LL)
Chloride	94–109 mmol/L	76 (L)
BUN	5–24 mg/dL	28 (H)
Creatinine	0.52–1.04 mg/dL	3.91 (H)
Glucose	60–99 mg/dL	43 (L)
Anion gap	6–17 mmol/L	43 (H)
Calcium	8.5–10.4 mg/dL	8.3 (L)
Albumin	3.9–5.1 g/dL	2.8 (L)
Protein, total	6.8–8.8 g/dL	6.0 (L)
AST	0–45 U/L	442 (H)
ALT	0–50 U/L	94 (H)
ALKPHOS	40–150 U/L	140
Bilirubin total	0.2–1.3 mg/dL	26.9 (H)
Bilirubin conjugated	0.0–0.3 mg/dL	
Lactic acid	0.7–2.1 mmol/L	15.3 (H)
Haematology		
White cell count	4.0–11.0×10^9/L	1.4 (L)
Red cell count	3.8–5.2×10^{12}/L	2.33 (L)
Haemoglobin	11.7–15.7 g/dL	8.1 (L)
HCT	35.0%–47.0%	23.4 (L)
MCV	78–100 fl	100
MCH	26.5–33.0 pg	34.8 (H)
MCHC	31.5–36.5 g/dL	34.6
RDW	10.0%–15.0%	15.6 (H)
Platelet	150–450×10^9/L	15 (LL)
% Neutrophils	40%–75%	48.5
% Lymphocytes	20%–48%	33.0
Absolute lymphocytes	0.8–5.3×10^9/L	0.5 (L)
Absolute monocytes	0.0–1.3×10^9/L	0.0
% Eosinophils	0%–6%	0.0
Absolute eosinophils	0.0–0.7×10^9/L	0.0
Absolute basophils	0.0–0.2×10^9/L	0.0
Ferritin	10–300 ng/mL	5932 (H)
Venous blood gas		
pH	7.32–7.43 pH	7.11 (LL)
PCO_2	40–50 mm Hg	28 (L)
PO_2	25–47 mm Hg	33
O_2 saturation	%	46
Bicarbonate	21–28 mmol/L	9 (LL)
Ionised calcium	4.4–5.2 mg/dL	3.5 (L)
Urinalysis	Latest reference range	
Colour		Dark brown
Appearance		Cloudy
Glucose	Neg mg/dL	30 (A)
Bilirubin	Neg	Large (A)
Ketones	Neg mg/dL	5 (A)
Specific gravity	1.003–1.035	1.019
pH	5.0–7.0 pH	5.0
Protein albumin	Neg mg/dL	30 (A)
Urobilinogen (mg/dL)	0.0–2.0 mg/dL	Normal
Nitrate	Neg	Negative
Blood	Neg	Small (A)
Leucocyte esterase	Neg	Trace (A)
White cell count	0–2/HPF	14 (H)
Red cell count	0–2/HPF	1
Bacteria	Neg/HPF	Few (A)
Squamous EPI/HPF	0–1/HPF	1
Transitional EPI/HPF	0–1/HPF	1
Toxicology		
Amphetamine qual	Neg (<500 ng/mL)	Negative
Barbiturates qual	Neg (<200 ng/mL)	Negative
Benzodiazepine qual	Neg (<200 ng/mL)	Negative
Cannabinoids qual	Neg (<50 ng/mL)	Negative
Cocaine	Neg (<300 ng/mL)	Negative
Opiates	Neg (<50 ng/mL)	Negative

ALKPHOS, alkaline phosphastase; ALT, alanine aminotransferase; AST, aspartate amintransferase; BUN, blood urea nitrogen; H, high; HCT, hematocrit; L, low; LL, critically low; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volumne; O_2, oxygen; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; RDW, red blood cell distribution width.

Unfortunately, she was hospitalised 3 months prior to her current presentation, before her scheduled rheumatology appointment, for new onset seizures with associated hepatitis, leucopenia and electrolyte abnormalities. At that time, she was given a presumptive diagnosis of alcohol withdrawal seizures and possible drug-induced lupus. Due to her abnormal liver enzymes, additional testing included negative serologies for hepatitis B, hepatitis C, antismooth muscle antibody, antimitochondrial antibody and HIV. An ultrasound of her liver was remarkable for a steatohepatitis.

At the time of her current admission, she was abstinent from alcohol and cocaine, although prior use of both was noted. She was an active smoker with approximately 20 pack years. She lived alone, had no children, and was self employed. Family history was obtained. Her mother was deceased and had a history of hypertension and arthritis. Father was also deceased. She had two sisters and two brothers, all of whom were healthy.

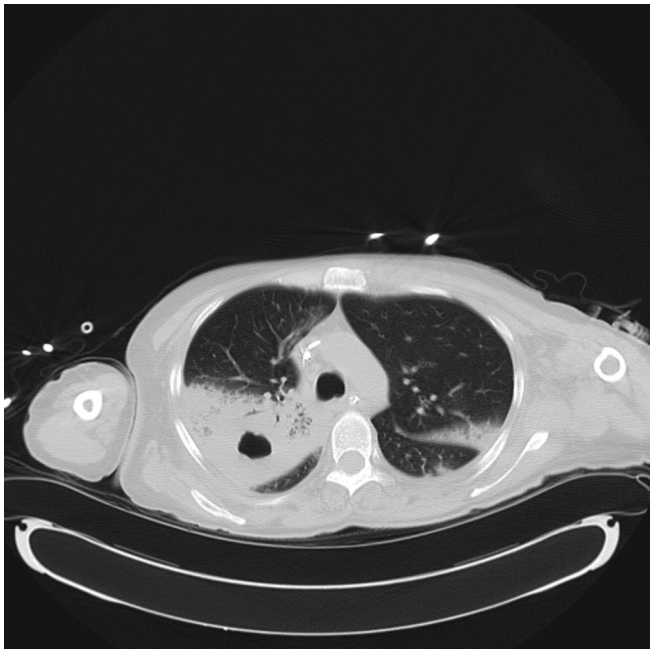

Figure 1 CT scan of the chest revealing consolidation with cavitary lesion in the right upper lobe.

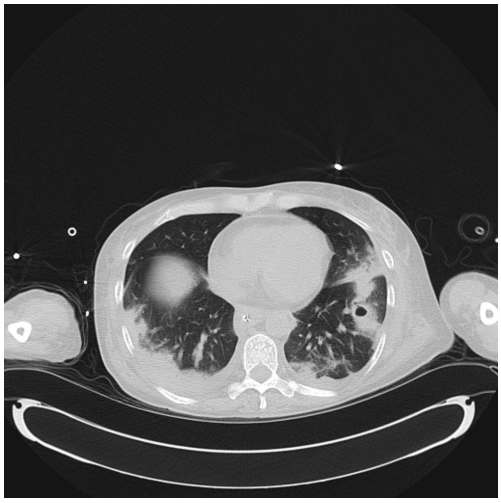

Figure 2 CT scan of the chest visualising cavitary lesion in the left upper lobe with associated ground glass opacities/consolidation.

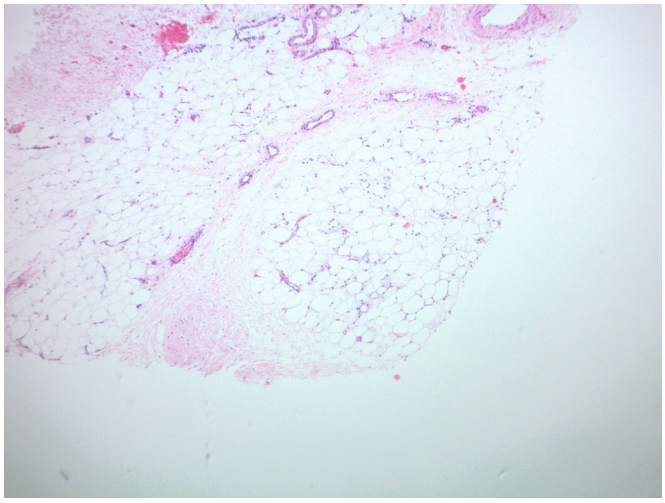

Figure 3 Punch biopsy of skin demonstrating fat necrosis with lipophages.

OUTCOME AND FOLLOW-UP

During this hospitalisation, laboratory work-up demonstrated rising titres of ANCA antibodies, this time with a titre of 1:1280. A confirmatory test for myeloperoxidase and serine protease 3 (PR3) returned positive with values of 362 Au/mL and 38 Au/mL, respectively. Additional rheumatological antibodies were negative (see table 2). Urinalysis showed scant red blood cells but no RBC casts. Cultures were sent, including blood, sputum and urine, all of which were negative. AAT levels and Pi typing were sent as part of her liver failure work-up, which showed an AAT level of 111 mg/dL (range 100–200 mg/dL) and a PiEE phenotype (ARUP Labs, Salt Lake City, Utah). Unfortunately, despite aggressive life support measures, the patient's clinical course continued to deteriorate. Her family elected to withdraw life-sustaining measures. A postmortem examination was declined by her family.

DISCUSSION

We describe a case of a 48-year-old woman presenting with hepatic failure and multiorgan dysfunction with a clinical picture of a progressive catastrophic ANCA-associated vasculitis in the setting of normal AAT levels and a rare homozygous phenotype 'EE'.

This is an unusual case for several reasons, including the uncommon AAT phenotype, the possible association with ANCA-associated vasculitis and the prior history and biopsy compatible with a diagnosis of panniculitis.

There are more than 100 variants of AAT with greater than 30 known deficient variants.[3] The finding of a homozygous phenotype 'EE' is, to our knowledge, the second reported case in the literature,[4] but the first to focus on an individual patient with the 'EE' phenotype.

The vast majority (95%–97%) of AAT in the human population is accounted for by three phenotypes: M (the wild-type protein), S and Z. Rare mutations as well as null phenotypes account for the remaining 3%–5%. The majority of literature for individuals with abnormal AAT alleles is focused on AAT deficiency which is most often defined as individuals who are homozygous for the 'Z' protein. There is a paucity of information and reporting regarding the clinical phenotypes of rare alleles.[4–6]

The most well studied and reported clinical associations of abnormal AAT protein variants include the lung (emphysema/COPD) and liver (hepatitis/cirrhosis) involvement that are seen in classic AAT deficiency (PiZZ).[6] The primary biological function of AAT is inactivation of proteolytic enzymes. It is primarily produced by hepatocytes and released into the circulation in a constitutive and inducible fashion.[2] AAT is an acute phase reactant protein, and levels increase four to six fold in the setting of acute inflammation.[7] Although the primary target is believed to be serine proteinase elastase, AAT is also capable of inactivating other neutrophil proteases, such as cathepsin G, proteinase 3, and myeloperoxidase.[2] The mechanism of emphysema associated with AAT deficiency is thought related to an imbalance between proteolytic enzymes and the neutralising effect of the AAT protein. Liver disease, including cirrhosis, is predominantly related to polymerisation of the Z protein within the hepatocyte due to protein miss-folding; this polymerisation results in hepatocyte injury.[6] Because our patient did not have AAT deficiency, these mechanisms were not thought to be applicable in this case.

The intrigue of our case presentation stems from our patient's presentation with ANCA-associated vasculitis and necrotising panniculitis in the setting of an abnormal AAT protein where the causal mechanism of disease is unclear. There is a growing body of

Table 2 Rheumatological and hepatic investigations

	Latest reference range	Reported Values
Hepatitis B surface antigen	Neg	Negative
Hepatitis B surface antibody	Neg	Negative
Hepatitis C antibody	Neg	Negative
HIV 1 and 2 antibodies	Neg	Negative
Antimitochondrial antibody	0–20 AU/mL	4.3
Antismooth muscle antibody	0–40 AU/mL	1
Antihistone antibody (3 months prior)		1.5 mg/dL
Alpha-1 antitrypsin (AAT)	100–200 mg/dL	111 mg/dL
Antimyeloperoxidase antibody	<1.0 U	362 (H)
Antiserine PR3 antibody	<1.0	38 (H)
ANCA (current admission)	<1:20	1:1280
ANCA (3 months prior)	<1:20	1:640

ANCA, antineutrophilic cytoplasmic antibody; H, high; L, low; LL, critically low; PR3, protease 3.

literature to suggest that the role of AAT in immune function and regulation extends far beyond that of the simple protease/antiprotease imbalance. Manifestations of a link between abnormal alpha-1 alleles and a dysregulated immune process are exemplified in cases of ANCA-associated vasculitis and necrotising panniculitis[8 9]

Development of ANCA-associated vasculitis has been previously described in AAT deficiency and is most strongly associated with homozygosity for the Z allele.[10–14] The most commonly reported association is granulomatosis with polyangitis[13] results from two large case series suggest the prevalence of any ANCA-associated vasculitis in patients with any AAT deficiency is approximately 1%–2%.[11–14] A proposed mechanism for development of autoantibodies in this setting is the reduced ability of AAT to neutralise PR3, which promotes proteolytic damage and triggers immunological development of autoantibodies.[15]

Necrotising panniculitis is an inflammatory condition of the subcutaneous tissues which results in the development of recurrent, painful rashes with erythematous plaques and ulcerating nodules, typically in the lower extremities and trunk.[2 3 6] It is extremely rare with an estimated prevalence of 1/1000 in individuals with AAT deficiency (PiZZ), though increasing case reports have documented associations with multiple alleles, with both heterozygotes and homozygotes affected. There appears to be a predilection for women with AAT aged 30–60.[16 17] The mechanism by which panniculitis occurs is unclear.

Identification of AAT was initially done via isoelectric focus assays, which identified AAT proteins by weight and diffusion and the nomenclature was developed related to how far the protein migrated across a gel. The 'E' protein product is an uncommon variant of AAT that is thought to result in normal serum concentrations and activity of the protein. Available reports indicate a median serum concentration of 156 mg/dL though the range is documented as 49–252 mg/dL (CI 95% of all observed serum concentrations).[2 4] On the basis of 'normal' levels of AAT, individuals with an 'E' allele protein are believed to be not at increased risk for developing AAT deficiency (PiZZ)-related pulmonary disease. Confounding this assertion is that very little to no information is known regarding the inhibitory activity or function of the 'E' protein.[4] Other AAT alleles, such as the "F" allele, produce dysfunctional proteins with reduced enzymatic activity. Patients with these variants are at risk of pulmonary disease despite normal levels of circulating AAT.[4 18] The recognition of dysfunctional proteins despite normal AAT levels has led to increased genetic testing of the SERPINA1 gene, which codes AAT in hopes of expanding our understanding of this complex relationship.[19] Unfortunately in our case, we were unable to obtain sequencing of the SERPINA1 gene, and confirmation of the mutation was not available. The evolving AAT literature frequently focuses on SERPINA1 genetics rather than isoelectric focus assays, although isoelectric focus assays are frequently what is clinically available.[19]

Our patient's history of rising ANCA titres, coupled with known sinus disease and new cavitary lung nodules, is compatible with the diagnosis of ANCA-associated vasculitis. The presence of necrotising panniculitis was suspected after careful history was obtained during her current admission. While her prior skin biopsy did not demonstrate classic findings of acute panniculitis, the demonstration of fat degeneration and accompanying inflammatory infiltrate was suggestive of a prior inflammatory process involving the panniculus.[20 21] We acknowledge confounding our patient's presentation was her history of prior drug use. Cocaine use can yield a similar syndrome of ANCA-associated inflammation, typically P-ANCA predominant but usually with both C-ANCA and P-ANCA antibodies present.[22–25] This was considered but was deemed unlikely. Not only was she abstinent from cocaine at the time of presentation, but her syndromal symptoms, such as palatal abnormalities and recurrent sinusitis, predated her cocaine use. It is plausible, however, that her prior drug use could have contributed as a potential immunological trigger in an individual with a possible genetic susceptibility. Although the finding of an unusual AAT protein and ANCA-associated vasculitis does not imply causality, the association provokes considerable intrigue and reconsideration of the potential inflammatory consequences abnormal alpha-1 protein variants may contribute to homeostasis beyond the protease:antiprotease paradigm.

Given that the American Thoracic Society guideline recommendations suggest screening of all patients with COPD and liver disease for AAT Deficiency,[1] it is likely that we will continue to see more patients diagnosed with AAT deficiency and will continue to find individuals with rarer, potentially non-deficient mutations. As we discover more AAT mutations and diagnose more patients, we will need to build on our current knowledge base to provide care for this unique population. We feel that the rarity of this mutation and its unknown impact on immune function and neutrophil elastase are precisely the key features that we wish to highlight and provoke discussion by presenting this case.

Learning points

We present a discussion of a middle-aged woman with a rare genetic mutation and catastrophic antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.

- Although alpha-1 antitrypsin (AAT) deficiency has been well described, less is known about rare alleles and their clinical presentation and disease associations.
- ANCA-associated vasculitis and panniculitis are rare but notable clinical manifestations associated with abnormal AAT alleles.
- There has not been a previously described report of PiEE AAT with ANCA-associated vasculitis.
- Given that the American Thoracic Society guideline recommendations suggest screening of all patients with chronic obstructive pulmonary disease and liver disease for AAT deficiency, it is likely that we will continue to see more patients diagnosed with AAT deficiency and increase the likelihood of finding individuals with rarer, potentially non-deficient mutations. As we discover more AAT mutations and diagnose more patients, we will need to build on our current knowledge base to provide care for this unique population.

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