CLINICAL VIGNETTE

LAZARUS 2.0
A case report of Alpha-1-Antitrypsin deficiency

Peter C. Galier, M.D.

"I can't believe it. I thought he was on death's door just last week when I saw him last."
"Yea, I know. That stuff brought him back to life."

A 39-year-old male transferred to SM-UCLA Medical Center from an out of state hospital for management of worsening, non-healing and ulcerating skin wounds, joint pain, and panniculitis. He had no significant past history. He had the usual childhood illnesses, but had no chronic or recurring illnesses.

He presented to his PMD one week after fresh water fishing in Texas. He developed red, painful swollen feet with painful nodules. He was initially placed on oral antibiotics, and when he showed no signs of improvement, Infectious Disease consultation was obtained. He was placed on parenteral Vancomycin and Cefepime via PICC line as an outpatient. He worsened and developed fever and polyarthalgias. Despite antibiotics, his symptoms persisted, and he also developed deep bruising on his thighs, axillae, and upper arms. These areas then blistered, crusted and became necrotic. They required surgical debridement, and wound vac placement. Studies at the outside hospital included: Venous Doppler showing left basilica and axillary vein thrombosis, likely secondary to the PICC line; CT of left upper extremity showing diffuse soft tissue edema but no muscle abnormality; MRI of femur showing the thigh wounds with a sinus tract, but no abscess; diffuse muscle engorgement compatible with myositis; and muscle biopsy of thigh, which was inconclusive.

Upon transfer to SM-UCLA Medical Center, additional work-up showed worsening pleural effusions, and multiple small pulmonary emboli. His panniculitis was so severe that any movement, dressing change or wound vac change required large doses of IV narcotics. He was seen by Rheumatology and autoimmune and immunodeficiency work-ups were negative. Alpha-1-antitrypsin (AAT) was considered, but the patient had no lung disease, liver disease, or recurrent childhood illnesses of suspicion. A level was sent, and it returned abnormal at 43, normal ranges being 83-199. His phenotype was ZZ.

Alpha-1-antiprotease was obtained and he was treated with 60mg/kg, with dramatic improvement of his panniculitis. All wound vacs were discontinued by discharge. His pleural effusions resolved, and his myalgias and arthralgias had resolved to the point where he was able to move and transfer on his own. He was left with severe de-conditioning, which would require short term, acute rehab.

This case was unusual. Most patients with a ZZ phenotype of AAT deficiency have early onset of pulmonary emphysema: in the 30's for smokers, and early 50's for non-smokers. Liver manifestations would have been the most common finding for him. 10-15% of adults with this genotype will have hepatic dysfunction, also more severe if a smoker[1].

Of the people with ZZ phenotype, 11% have had a history of neonatal jaundice, or ascites, or bleeding issues[2], none of which applied to him. His neonatal and childhood medical history was negative.

Patients with AAT deficiency have been followed since childhood. Most had no evidence of clinically active liver disease by age 18, and only 12% showed minimal chronic elevations of the ALT or GGT[3].

Rarely, adults have developed chronic hepatitis or hepatocellular carcinoma with no history of childhood disease[4]. The prognosis for liver disease worsens with male gender and obesity, but interestingly, not for histories of alcohol use or viral hepatitis[5].

Skin disease, whose major manifestation in AAT deficiency is necrotizing panniculitis, is rare, and even more so as the initial presenting symptom. The more common cutaneous manifestations are vasculitis, urticaria, and angioedema[6]. The average age of onset of skin manifestations is 40, and the usual presentation is painful, red nodules or plaques, often with a yellow, greasy discharge thought to be

due to the adipose breakdown[7]. This can be missed on routine biopsy of affected areas, since most of the findings are in the deep subcutaneous fat near the muscles. Typical findings are lobular fat necrosis and neutrophilic invasion[6]. Other manifestations of the ZZ phenotype include abdominal and intracranial aneurysms, as well as ANCA positive vasculitis[8, 9]. One case controlled study found a statistically significant increase in ulcerative colitis in patients with AAT deficiency[10]. Glomerulonephritis was also found in a number of AAT deficient patients, but all had associated liver disease, raising the question of whether the deficiency itself was a cause, or if the hepatic disease was the cause in another fashion, such as an immune complex process[11].

Our patient was given 3 doses of AAT infusion at 60mg/kg for a total of 6 grams each time. He had dramatic clinical improvement. Skin lesions essentially resolved, as did his pleural effusions and general anasarca. He will be getting weekly infusions as an outpatient. Studies confirm that weekly infusions keep AAT levels high enough to be protective. Several studies using larger, less frequent dosing did not provide sufficient levels to maintain protection[12].

REFERENCES

1. **Tanash HA, Nilsson PM, Nilsson JA, Piitulainen E**. Clinical course and prognosis of never-smokers with severe alpha-1-antitrypsin deficiency (PiZZ). *Thorax*. 2008 Dec;63(12):1091-5. doi: 10.1136/thx.2008.095497. Epub 2008 Aug 5. PubMed PMID: 18682522.
2. **Sveger T**. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. *N Engl J Med*. 1976 Jun 10;294(24):1316-21. PubMed PMID: 1083485.
3. **Sharp HL, Bridges RA, Krivit W, Freier EF**. Cirrhosis associated with alpha-1-antitrypsin deficiency: a previously unrecognized inherited disorder. *J Lab Clin Med*. 1969 Jun;73(6):934-9. PubMed PMID: 4182334.
4. **Zhou H, Ortiz-Pallardó ME, Ko Y, Fischer HP**. Is heterozygous alpha-1-antitrypsin deficiency type PIZ a risk factor for primary liver carcinoma? *Cancer*. 2000 Jun 15;88(12):2668-76. PubMed PMID: 10870048.
5. **Bowlus CL, Willner I, Zern MA, Reuben A, Chen P, Holladay B, Xie L, Woolson RF, Strange C**. Factors associated with advanced liver disease in adults with alpha1-antitrypsin deficiency. *Clin Gastroenterol Hepatol*. 2005 Apr;3(4):390-6. PubMed PMID: 15822045.
6. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med*. 2003 Oct 1;168(7):818-900. PubMed PMID: 14522813.
7. **Stoller JK, Piliang M**. Panniculitis in alpha-1 antitrypsin deficiency. *Clin Pulm Med* 2008; 15:113.
8. **Geraminejad P, DeBloom JR 2nd, Walling HW, Sontheimer RD, VanBeek M**. Alpha-1-antitrypsin associated panniculitis: the MS variant. *J Am Acad Dermatol*. 2004 Oct;51(4):645-55. Review. PubMed PMID: 15389208.
9. **Esnault VL, Testa A, Audrain M, Rogé C, Hamidou M, Barrier JH, Sesboüé R, Martin JP, Lesavre P**. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int*. 1993 Jun;43(6):1329-32. PubMed PMID: 8315946.
10. **Elzouki AN, Eriksson S, Löfberg R, Nässberger L, Wieslander J, Lindgren S**. The prevalence and clinical significance of alpha 1-antitrypsin deficiency (PiZ) and ANCA specificities (proteinase 3, BPI) in patients with ulcerative colitis. *Inflamm Bowel Dis*. 1999 Nov;5(4):246-52. PubMed PMID: 10579117.
11. **Davis ID, Burke B, Freese D, Sharp HL, Kim Y**. The pathologic spectrum of the nephropathy associated with alpha 1-antitrypsin deficiency. *Hum Pathol*. 1992 Jan;23(1):57-62. PubMed PMID: 1544671.
12. **Barker AF, Iwata-Morgan I, Oveson L, Roussel R**. Pharmacokinetic study of alpha1-antitrypsin infusion in alpha1-antitrypsin deficiency. *Chest*. 1997 Sep;112(3):607-13. PubMed PMID: 9315791.

Submitted on March 4, 2013