

CLINICAL VIGNETTE

Alpha-1-Antitrypsin Deficiency: A Rare Cause of Liver Disease in Community Hepatology Practices

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Case

A 34-year-old male with a past medical history of small bowel obstruction, tubular adenoma of colon, external hemorrhoids, migraine headaches presented to an outpatient gastroenterology for of right sided abdominal pain and changes in bowel habits. When he is feeling well he has one formed bowel movement per day. Since becoming symptomatic his stools became dark and tarry with increased frequency, three times a day for the past 2 months. Complete metabolic panel previously ordered by his neurologist was noted to have a mild elevation of his alanine aminotransferase, 83 U/L. He denied drinking alcohol. A repeat liver panel was obtained one month later and showed persistent elevation of his ALT, 80. Chronic liver disease testing found low level of serum alpha-1-antitrypsin. Subsequently isoelectric focusing found him heterozygous for the Z mutation for alpha-1-antitrypsin deficiency, genotype MZ. Abdominal ultrasound revealed normal liver morphology and an absence of gallstones. Upper endoscopy did not show any evidence of portal hypertension, only reflux esophagitis and mild gastritis. He was then referred to pulmonology to establish baseline pulmonary function tests as well as to screen for emphysema.

Discussion

Alpha 1 anti-trypsin deficiency (AATD) is a rare cause of liver disease, but is considered to be common but underdiagnosed.¹ It is most often seen in patients of North-Western European decent. The protein alpha-1-antitrypsin is encoded by the SERPINA1 gene on chromosome 14. Alpha-1-antitrypsin is manufactured predominately in the liver but also can be found in erythrocytes, some mononuclear white blood cells, bone marrow, pulmonary alveolar cells and Paneth cells of the gut.² The normal function of alpha 1 anti-trypsin is to act as a protease inhibitor to prevent degradation cells by various inflammatory cell enzymes, particularly neutrophil elastase and trypsin.³ Alpha-1-antitrypsin normally undergoes folding in the endoplasmic reticulum (ER) of a hepatocyte and then is secreted out of the cell within minutes of its synthesis. The normal genotype is the M allele. Patients with mutations referred to as "S" or "Z" alleles, which are identified by isoelectric focusing, are at risk for developing the disease. AATD is most commonly seen in patients homozygous for the Z allele. However, much less frequently, heterozygotes of Z or S alleles, are found with lower severity of disease. The heterozygous MZ genotype is seen in 4% of the population of European decent, making it a much more common form seen in

clinical practice.⁴ In patients that are homozygous for the Z allele, nearly 85% of the alpha-1-antitrypsin protein is folded incorrectly in the ER, resulting in accumulation of the ZZ alpha-1-antitrypsin proteins into large polymers that result in hepatotoxicity. On liver biopsy, these large polymers stain positively with periodic acid-Schiff stain.⁵ The lack of alpha-1-antitrypsin in the serum results in unchecked neutrophil elastase, allowing it to freely break down elastin in the lungs.² This degradation of elastin results in a loss of elasticity of the lungs, leading to conditions such as emphysema and/or chronic obstructive pulmonary disease (COPD). NSAIDs and smoking, even if second hand, are particularly toxic in ZZ homozygous patients.² Oxidants found in cigarette smoke cause the oxidation of the active site of the alpha-1-antitrypsin protein, causing it to polymerize and rendering it inert.⁴ Polymerized Z alpha-1-antitrypsin is also a potent neutrophil chemoattractant, resulting in higher levels of unopposed neutrophil elastase.⁶ Patients with alpha-1-antitrypsin deficiency should be referred to pulmonology at age 18 for baseline evaluation. Patients with heterozygous MZ genotype are less likely to develop liver disease unless another underlying liver pathology is present, such as: non-alcoholic fatty liver disease, alcoholic liver disease or cystic fibrosis.⁴ However MZ genotypes are known to have an increased incidence of gallstone disease and ANCA associated vasculitis.⁷

Currently there is no curative treatment for alpha-1-antitrypsin deficiency. Alpha-1-antitrypsin is available as an infusion composed of concentrate from blood plasma from human donors. It can be given once weekly to patients with lung disease. Currently no therapy is available for the treatment of liver disease seen in alpha-1-antitrypsin deficiency other than liver transplant for those that progress to cirrhosis.

Conclusion

Alpha-1-antitrypsin deficiency is a rare genetic disease caused by an amino acid substitution resulting in improper folding of the protein leading to retention within the hepatocytes. Despite its rarity, it is common when evaluating abnormal liver panels. Heterozygotes of the Z allele typically have normal hepatic and pulmonary function unless environmental or other confounding diseases are present. Gastroenterologists in the community should be aware of the higher risk MZ phenotypes have for cholelithiasis and thus have a low threshold to evaluate biliary

colic and acute cholecystitis. Liver transplantation remains the only therapy available for those patients with hepatic disease that progresses to cirrhosis. Consequently, gastroenterologists should refer patients homozygous for ZZ phenotype to tertiary referral centers with transplant hepatology services for routine surveillance should the need for liver transplantation arise.

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