

CLINICAL VIGNETTE

Abnormal Liver Function Test in an Older Adult – Could this be Alpha-1 Antitrypsin Deficiency?

Steven Kind, MD and Gabriela Sauder, MD

Case Presentation

A 77-year-old male was referred to Gastroenterology for co-management of recurrent diverticular disease and mild, chronic elevations in transaminases and alkaline phosphatase, with normal liver synthetic function. The patient has Chronic Lymphocytic Leukemia/Small Cell Lymphocytic Lymphoma, CLL/SLL which was diagnosed 4 years ago and was actively treated initially with bendamustine, rituximab, and most recently acalabrutinib which was discontinued 6 months prior to referral. He has chronic, long-standing thrombocytopenia in the 80-100k range for nearly 50 years. Other problems include: gout, recurrent UTI and interstitial cystitis, recurrent diverticulitis and recent colonic resection for colovesicular fistula presumed due to diverticular disease.

His CLL/SLL is Stage IIIA. The initial CT abdomen and pelvis demonstrated numerous abdominal lymph nodes. FNA showed atypical lymphoid infiltrate, and surgical excisional biopsies showed evidence of immunophenotype CD5 positive, CD20 positive, BCL-2 positive compatible with CLL/SLL with Ki-67 20%, markers CD38 negative, ZAP70 positive, ATM (11q), 13q- deleted, and IgVH unmutated, with no B symptoms.

Patient reported two drinks of alcohol/day, no cigarette smoking, and no occupational hepatotoxin exposure. He is active, hiking, and running about 1 hour most days, and completed ten marathons. There was no family history of lung or liver disease.

His recurrent diverticulitis for the past few years was generally treated with oral antibiotics. The most recent episode about six months ago was more severe and required hospitalization. His platelets decreased to 45,000 from his baseline of 80-100k. Hospital imaging included CT abdomen and pelvis that revealed mild perihepatic ascites, and cholelithiasis, and labs showed chronic mild elevations in AST, ALT and alkaline phosphatase, with normal liver synthetic function. Follow-up CT A/P demonstrated a heterogeneous appearing liver with slightly nodular contour, borderline splenomegaly with perigastric and periesophageal collaterals and small volume ascites.

On review of systems, the patient reports intermittent abdominal distension, early satiety/lack of appetite, but denies fatigue, nausea/vomiting, or jaundice. The patient denies weight loss,

dyspnea with exertion or at rest, cough, wheezing, or repeated episodes of bronchitis.

His medication list includes allopurinol, and a multivitamin.

On physical exam, he is a well appearing man. His cardiac, pulmonary, abdominal exams were normal, and he has mild bilateral lower extremities edema, but no jaundice, rashes, or other stigmata of chronic liver disease.

His laboratory results are remarkable for CBC with platelets of 60,000. Comprehensive Metabolic Panel was notable for alkaline phosphatase of 225, AST of 54 and ALT of 46, with normal albumin and bilirubin. Hepatitis serologies were negative, ceruloplasmin was normal, ANA <1:40, ASMA <1:20, AMA <1:20, celiac serologies neg, IgA 94, AFP 4.5, Ca 19-9 38, and HFE gene mutation analysis negative. The alpha 1 antitrypsin level A1AT was low at 22 (N 90-200 mg/dL), and he was a homozygote for Pi-ZZ phenotype. Shear wave liver stiffness measurement indicated advanced fibrosis and/or cirrhosis with MetaVir stages F4 and some F3. His MELD score was 9 and Child Pugh 6A indicating well compensated disease.

EGD reported normal findings without esophageal or gastric varices. Colonoscopy limited to transverse colon showed intact anastomosis at 12cm, diverticulosis and internal hemorrhoids.

Discussion

Alpha-1 antitrypsin deficiency (A1ATD), is one of the most common genetic diseases, yet remains under-diagnosed likely due to either lack of clinical manifestations despite severe deficiency, or not being recognized in symptomatic patients. The prevalence of severe A1ATD among patient with emphysema and COPD varies between 1% to 4.5%,^{1,2} while the prevalence of liver cirrhosis in severe A1ATD with PIZZ phenotype varies between 20-35%.³

Risk factors for advanced liver disease include male gender, obesity, and presence of metabolic syndrome. Alcohol consumption promotes the progression of the disease.⁴ Risk factors for developing severe emphysema are serum level of A1AT below 11 micromol/L, cigarette smoking, dusty occupational exposure, parental history of COPD, and personal history of asthma, chronic bronchitis, or pneumonia.⁵ Other manifesta-

tions of AATD are neutrophilic panniculitis, ANCA-associated vasculitis, abdominal and intracranial aneurysms and arterial fibromuscular dysplasia, proliferative glomerulonephritis and IgA nephropathy and inflammatory bowel disease.⁴ A1ATD is an autosomal co-dominant disorder, encoded by the protease inhibitor (Pi) locus on chromosome 14q32.1, and caused by mutations in the *SERPINA1* gene. Over 200 mutations of the *SERPINA1* have been identified.^{5,6} The normal genotype is PiMM. The serum levels of alpha-1 antitrypsin and some of the more common genotypes are: PiSS is at 60% of normal serum level, PiSZ is at 40%, and PiZZ is at 10-15% of normal serum level of alpha-1 antitrypsin.

The role of AAT is to neutralize proteolytic enzymes, such as neutrophil elastase, and to protect the breakdown of the matrix proteins of the lung like elastin. In the absence of this protective effect of AAT, there is unopposed proteolytic burden which may result in emphysema labeled as “toxic loss of function.” In the liver, point mutations in the Z protein can lead to retention and accumulation of AAT in the hepatocytes, resulting in activation of an intracellular injury cascade and hepatocytes apoptosis with compensatory hepatocellular proliferation and fibrosis, or “toxic gain of function.”⁷

The onset of lung disease is typically between 20 and 50 years old, when patients may present with shortness of breath, wheezing and are at increased risk for lung infections.² The onset of liver disease can be variable, with about 40% of the adults with P PiZZ genotype developing liver disease, including chronic hepatitis, cirrhosis, or hepatocellular carcinoma.⁶

The diagnosis of A1ATD is confirmed by a low serum level of AAT by nephelometry, with severe deficiency below 11 micromol/L in combination with a severe deficient phenotype determined by isoelectric focusing, or genotype, assessed by testing for the deficient alleles (ie, S, Z, I, F). Evaluation for pulmonary manifestations of A1ATD should include pulmonary function tests to assess the presence and severity of lung disease, and chest imaging to evaluate for emphysema.

Evaluation of liver disease in A1ATD, should include laboratory tests for liver function, and abdominal ultrasound-based elastography. Ultrasound elastography is increasing used as an alternative to liver biopsy to assess hepatic fibrosis, and to predict complications in patients with cirrhosis. This method grades liver fibrosis on a scale of F0 to F4, with F4 indicating advanced fibrosis and/or cirrhosis.

Patients with A1ATD should be monitored closely, and have CBC, CMP, prothrombin time and alpha-fetoprotein every 6 months, as well as screening for hepatoma with ultrasound. If cirrhosis is present, annual upper endoscopy screening for varices is recommended.

Preventative measures include vaccinations for hepatitis A and B, influenza and pneumococcal vaccine. Patients should stop smoking; avoid alcohol, and avoid hepatotoxic drugs. They should eliminate raw seafood and shellfish from their diet.

Treatment of lung disease consists of IV augmentation therapy of pooled human alpha-1 antitrypsin protein. Patients with liver disease can be considered for transplantation as curative therapy.

Conclusion

A1ATD is a common, under-recognized genetic disease. The clinical manifestations are variable and heterogeneous. Many patients may remain asymptomatic, or only have mild abnormalities in their liver function tests. Alcohol consumption, polypharmacy, and drug disease interactions may accelerate the progression of the liver disease.

The American Thoracic Society (ATS) Guidelines recommend testing for AATD in all patients with COPD, liver disease, poorly responsive asthma, c-ANCA vasculitis related to proteinase 3 antibody, panniculitis, bronchiectasis, and first-degree relatives of patients with AAT deficiency.^{1,2} At this time, there is no specific treatment of A1ATD-associated liver disease. Supportive measures and regular monitoring are advised with consideration of liver transplant for patients with advanced disease.

The evaluation for abnormal biochemical and functional liver tests should follow a step-wise approach, starting with grouping the patterns of abnormal liver test into three categories: hepatocellular, cholestatic, or isolated hyperbilirubinemia. Liver synthetic function is evaluated by serum albumin, and PT/INR. It is important to determine the length of time abnormalities have been present to classify as acute, subacute or chronic. Patients should be evaluated for other causes of liver disease including: celiac disease, viral hepatitis, autoimmune liver disease, Wilson’s disease, hemochromatosis and alpha-1 antitrypsin deficiency.

Diagnosis of A1ATD and liver cirrhosis no longer requires liver biopsy, as ultrasound-based elastography can be used to assess and monitor hepatic fibrosis, and to predict complications in patients with cirrhosis.

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