Acute liver failure secondary to amyloid light-chain amyloidosis- case report

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Abstract:

Amyloidosis is a systemic disease characterized by diffuse deposition of amyloid proteins in multiple organs(1). Although the liver is a common site of involvement in amyloidosis, the clinical presentation of hepatic involvement is typically mild, and rarely manifests as hepatic failure. This is a report of a 44-year-old Caucasian male who presented with acute liver failure secondary to amyloid light-chain (AL) amyloidosis. Consent was obtained from the patient's family.

Key words:

Acute liver failure, Amyloidosis

Case Presentation:

A 44-year-old male with a past medical history of hypertension, hyperlipidemia, and no history of alcohol or drug abuse was admitted to the hospital with a five-month history of jaundice, nausea, vomiting, and abdominal pain. His review of systems was notable for fatigue, anorexia, and weight loss of 70 lbs. over a 7-month period. Physical exam revealed severe jaundice and tender hepatomegaly with the liver margin 4 cm below the right costal margin. No ascites or peripheral adenopathy were noted. Upon admission, laboratory studies and urine tests were as follows:

Lab test	Lab Value	Normal Range
White blood cell (WBC)	**13.7x10^3/µL**	4.5 to 11.0x10^3/µL
Hematocrit (HCT)	**32%**	34.9 to 44.5%
platelets count	200x10^3/µL	150 to 450 x10^3/µL
Alanine aminotransferase (ALT)	**377** U/L	7 to 56 U/L
Aspartate aminotransferase (AST)	**498** U/L	10 to 40 U/L
Alkaline phosphatase (ALP)	**1,471** u/L	44 to 147 u/L
International Normalized Ratio (INR)	**3.20**	< 1.1
Total protein	**4.2** gm/dL	6 and 8.3 gm/dL
Total albumin	**2.7** gm/dL	3.5 to 5.5 gm/dL
Total bilirubin	**34.0** mg/dL	0.1 to 1.2 mg/dL
Bilirubin direct	**22.84** mg/dL	< 0.3 mg/dL
Blood urea nitrogen (BUN)	**27** mg/dL	7 to 20 mg/dL
Creatinine	**5.69** mg/dL	0.6 to 1.2 mg/dL
Ammonia	**89** µmol/L	16-53 µmol/L

Blood studies revealed normal free kappa light chain, elevated free lambda light chain, decreased kappa/lambda ratio, with normal serum protein electrophoresis. Serologies for viral hepatitis were unremarkable. Autoimmune work-up including antinuclear, anti-smooth muscle, and anti-DNA antibodies were also negative.

Ultrasound imaging of the abdomen demonstrated an enlarged liver measuring greater than 20.3 cm in the craniocaudal dimension with otherwise normal echogenicity. No definite focal hepatic lesions or dilated intra or extrahepatic biliary radicles were noted. Also, the hepatic vasculature was patent. Given unrevealing etiological work up, the patient underwent transjugular liver biopsy, which showed extensive amyloid deposition within hepatic sinusoids that stained with Congo red (Fig.1. and fig.2.). The hepatic architecture, including portal tracts and central veins, was intact. Additionally, the hepatocytes were shrunken in appearance with decreased cytoplasm and an overall atrophic appearance. Amyloid protein identification identified AL (lambda)-type amyloidosis. Subsequently, a bone marrow (BM) biopsy demonstrated cellular marrow with trilineage hematopoiesis and a plasma cell neoplasm >10% with marked interstitial amyloid deposit. Echocardiography revealed left ventricular hypertrophy (LVH), apical sparing by strain imaging, very low tissue Doppler velocities, and speckled appearance of the myocardium. These findings were consistent with an infiltrative cardiomyopathy. One month after liver biopsy confirmed a diagnosis, the patient developed encephalopathy and

received standard dose of rifaximin and lactulose.

Given the constellation of clinical and pathologic features that support a diagnosis of AL amyloidosis secondary to plasma cell malignancy, the patient was also started on a weekly standard dose of cyclophosphamide, bortezomib, and dexamethasone**.** His hospital course was complicated by acute renal failure likely due to renal amyloidosis that required continuous renal replacement therapy (CRRT). We avoided renal biopsy because it would not affect management and potentially high risk of hemorrhage in the setting of underlying coagulopathy. Our patient also exhibited tachycardia with intermittent bradycardia; given his elevated transaminases, amiodarone was avoided, and his bradycardia limited our ability to use beta blockers for rate control. Unfortunately, the patient developed multi-organ failure and shock. Due to his "Do Not Resuscitate" status, this multi-organ failure led to his death.

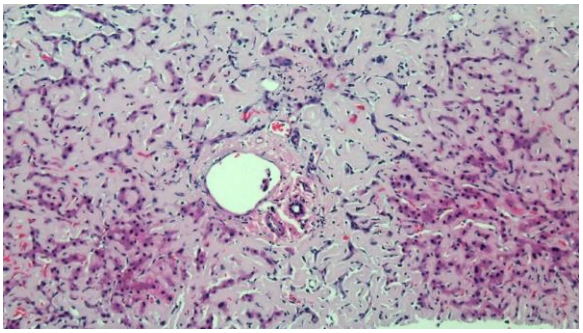

Fig.1. At low power, an intact portal tract is seen at the center with surrounding lobules showing markedly distended sinusoids filled with amyloid

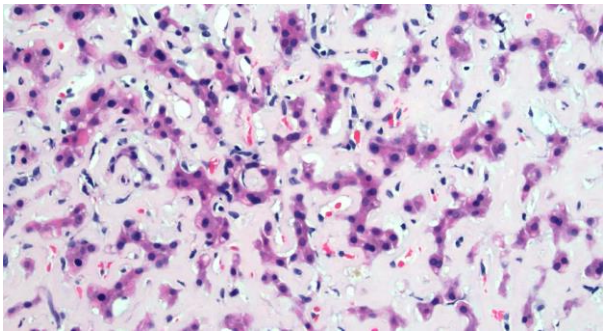

Fig.2. A higher power image highlights anastomosing cords of atrophic hepatocytes surrounded by amyloid. Occasional red blood cells can be seen within the residual sinusoidal spaces

Discussion:

Amyloidosis is defined by the accumulation of extracellular fibril deposits within organs and tissues. These amyloid proteins can stain with Congo red due to their characteristic beta-pleated sheets.(1) Though AL amyloidosis is a rare disorder, it is the most common form of amyloidosis followed by: secondary, localized, familial and senile forms.(2)

AL amyloidosis has been classified as either primary amyloidosis or myeloma-associated amyloidosis. Primary amyloidosis constitutes the vast majority of AL amyloidosis.(3) AL amyloidosis may involve the largest range of organs, with the kidney and heart being the most commonly involved.(4) The gastrointestinal (GI) tract involvement is most notable in the small bowel and liver. Hepatic deposition is a common consequence of amyloidosis; an autopsy study showed that 70% of patients with AL amyloidosis have liver involvement.(5) However, hepatic amyloidosis rarely presents clinically as acute liver failure.(6)

The term acute liver failure has been used to describe the development of coagulation abnormality, usually an International Normalized Ratio (INR) ≥1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks.(7)

For a patient with non-specific, constitutional symptoms and hepatomegaly, hepatic amyloidosis may not frequently be considered in the differential diagnosis. However, in the context of an appropriate constellation of abnormal lab findings, hepatic amyloidosis warrants careful consideration as an etiologic entity. Lab findings hinting to a possible diagnosis of hepatic amyloid involvement include proteinuria, which is observed in 88-89% of patients with hepatic amyloidosis.(8) Additional clues include an elevated ALP level; in fact, an elevated ALP has been identified as the single most significant discriminating factor between hepatic and non-hepatic amyloidosis.(9) The patient presented here possessed abnormal trace urine protein and an ALP of 1,471 units/L.

In all published cases of ALF secondary to amyloidosis, the biochemical pattern was cholestatic, with a median total bilirubin level of 265 µmol/L (15.2 mg/dL) and a median ALP level of 1,132 IU/L. The elevation in total bilirubin level was predominantly of direct type in nearly all cases.(10)

AL amyloidosis can be diagnosed through serum protein electrophoresis with immunofixation electrophoresis (SPEP/IFE). However, about a quarter of those affected by amyloidosis will appear normal when screened with SPEP/IFE. This discrepancy can occur when pathogenic light chains are undetectable in serum because they are either made in small amounts or are filtered out by the kidneys. This likely explains why this patient's blood showed elevated free lambda light chain with normal serum protein electrophoresis. A more effective screening technique with a sensitivity of 90% involves a 24-hour urine collection paired with SPEP/IFE. Another diagnostic screening now available is the serum free light chain assay, which can detect minute levels of free light chains. Light chain levels are abnormal in 99% of AL amyloidosis cases.(11) All diagnostic tools require tissue biopsy confirmation.(12)

The median survival of AL amyloidosis patients is one to two years. This is the lowest survival rate of all forms of amyloidosis.(2) However, this prognosis depends greatly on organ involvement. For example, with major kidney involvement, the median survival rate is 21 months. In comparison, multi-organ involvement, especially cardiac involvement, has a median survival rate of 6 months.(13) This patient had multi-organ involvement.

Previous studies have identified three predictors of shortened survival in patients with hepatic amyloidosis, namely: heart failure, a platelet count > 500 X 10^9, and total bilirubin > 36 µmol/L. While echocardiography revealed normal systolic function and platelet counts were normal, this patient did present with a total bilirubin value of 612 µmol/L, which exceeds the threshold established for poor prognosis. Previous studies have demonstrated that the median survival of patient with primary (AL) hepatic amyloidosis is 1 month for those with a serum total bilirubin > 36 µmol/L compared to 15.6 months for those with a

serum total bilirubin within the reference range.(14) This patient's death, which occurred 28 days after initial diagnosis and subsequent treatment, was predicted by the serum total bilirubin threshold established by Park et al.(15)

There is currently no effective cure for hepatic amyloidosis aside from emergency liver transplantation.(16) Patients who do not receive liver transplants have a 15% 1-year survival rate.(17) Those who do receive transplantation have a 79% 1-year survival rate. A more recent, promising treatment regimen consisting of cyclophosphamide, bortezomib, and dexamethasone (often used for myeloma) has seen a 54% response rate in AL amyloidosis patients, though not specifically hepatic amyloidosis patients. Unfortunately, the median response time for this cytotoxic chemotherapy is 7.5 weeks, and this patient died 28 days after diagnosis and subsequent treatment.(18)

Conclusion:
This case highlights the importance of considering amyloidosis in the differential diagnosis of a patient presenting with obstructive jaundice and hepatomegaly, particularly in patients with proteinuria, and/or cardiomyopathy. Furthermore, it reveals the potential for hepatic AL amyloidosis to manifest clinically as acute liver failure. Knowing that hepatic amyloidosis can progress to acute liver failure may help guide optimal management and therapy. Those patients are not usually candidates for hepatic transplantation, and their management is challenging due to comorbid cardiac involvement and poor tolerance to chemotherapy. Studies are needed to help guide management of these cases.

Disclosure: None

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