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Fellows' Corner

Acute Liver Failure in a Patient with Cholestatic Liver Disease and Nephrotic Syndrome

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CASE PRESENTATION

A 52-year-old woman with hypertension presented to the hospital with months of poor appetite, 20-pound weight loss, and two weeks of bilateral leg swelling. She had no fever, shortness of breath, chest pain, abdominal pain, hematochezia, or melena. Prior outpatient workup included an echocardiogram, cardiac stress test, upper endoscopy, and colonoscopy, which were unremarkable. The patient had no history of alcohol, over-the-counter medication, recreational drug, or tobacco use. Family history was only significant for gastric cancer in her father. The vital signs were within normal limits on presentation, and the physical exam was unremarkable except for +3 lower extremity edema.

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Labs were significant for markedly elevated alkaline phosphatase (ALP) 4018 U/L (from 160 U/L three months prior and 11 U/L ten months prior), with elevated gamma-glutamyl transferase (GGT) of 717 mg/dl, AST 176 U/L, ALT 69 U/L, and total bilirubin 1.8 mg/dL (direct bilirubin 1.0 mg/dL; total bilirubin was normal two months prior). INR was normal at 1.08. The patient also had a creatinine 2.88 mg/dL (normal at baseline 3 months prior), blood urea nitrogen 51 mg/dL, and hypoalbuminemia 1.7 g/dL. The urinalysis was notable for proteinuria >500 mg/dL. Peripheral blood smear showed Howell-Jolly bodies, suggestive of splenic dysfunction. An abdominal ultrasound showed coarse hepatic echotexture and bilateral echogenic kidneys consistent with renal disease. A computed tomography pan-scan without contrast revealed hepatomegaly, mild mesenteric panniculitis ("misty mesentery"), and mild anasarca. Her labs progressively worsened during her hospital stay, particularly the total bilirubin (peak 26.6 mg/dL), which prompted further evaluation with magnetic resonance cholangiopancreatography, which showed no

choledocholithiasis and a normal biliary tree.

An extensive liver disease workup was performed. Labs were significant for positive ANA (1:600 titer) and low ceruloplasmin 4 mg/dL. Otherwise, the chronic liver disease workup was unremarkable, including viral hepatitis serologies, antimitochondrial antibody, anti-smooth muscle antibody, liver-kidney microsome type 1 antibody, soluble liver Ag IgG. Serum ferritin was 227 µg/mL, but iron saturation was 22%, likely secondary to an acute inflammatory state. Immunoglobulin G level was normal. The liver elastography showed a METAVIR stage F3 appearance (7.6 kPa). Further diagnostic workup was pursued.

Despite reaching a diagnosis and starting treatment, the patient continued to have worsening liver function and eventually developed liver failure with INR 1.61 and encephalopathy. Her kidney injury also progressed to end-stage renal disease requiring hemodialysis. Within a month of admission, the patient succumbed to her illness.

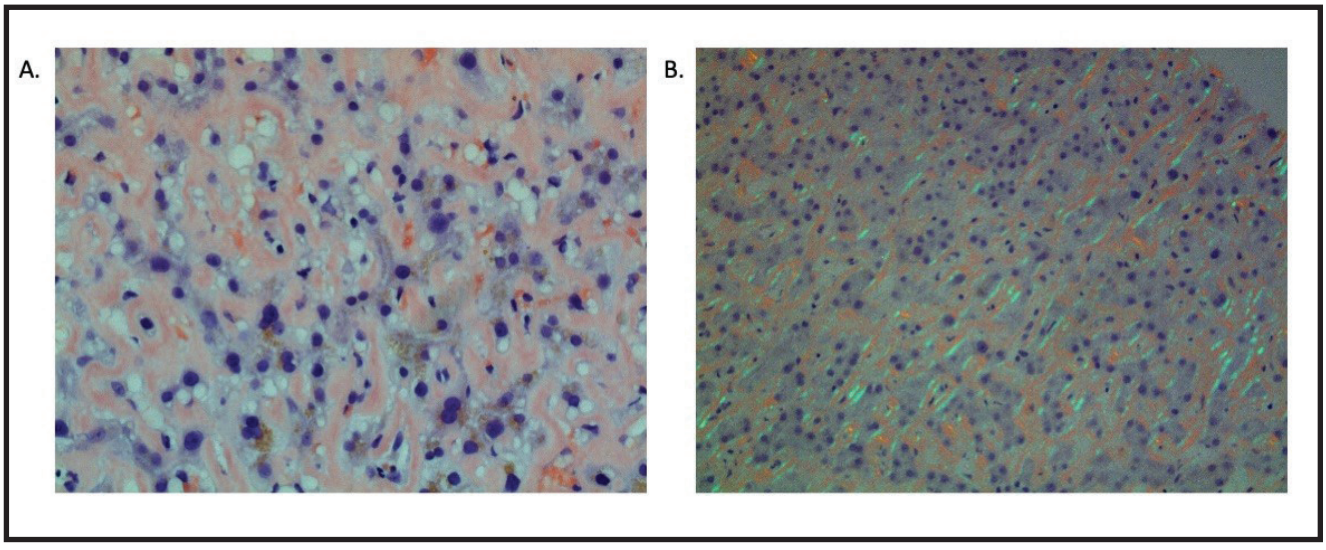
QUESTIONS

1. What are the differential diagnoses and what is the most likely diagnosis in this patient?

This patient had a cholestatic pattern of liver injury without evidence of apparent extrahepatic obstruction. In this case, we should consider other causes of cholestatic disease. Given the patient's lack of alcohol or medication use, the suspicion for alcohol and medication-induced cholestasis is low. Therefore, intrahepatic pathology should be considered. There was suspicion for autoimmune causes such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). PSC has also been associated with mesenteric panniculitis, better known as sclerosing mesenteritis, as described in this patient's imaging. AMA antibody was negative and IgG4 levels were normal, making the diagnosis of PBC and autoimmune cholangitis much less likely; however, small-duct PSC was still a possibility.[1] While ceruloplasmin was significantly low, one would think of Wilson's disease (WD), however given the highly elevated ALP and nephrotic syndrome in our patient, the hypoceruloplasminemia is much less likely due to WD and more likely due to protein loss from nephrotic syndrome.

It should be noted that at this point, our patient had two end-organ injuries, including acute kidney injury with nephrotic syndrome, prompting consideration of infiltrative diseases with systemic involvement, such as sarcoidosis or amyloidosis. Hepatic sarcoidosis manifests with noncaseating liver granulomas. The lack of characteristic sarcoid pulmonary and skin involvement made

Figure 1. Liver Biopsy
A. Dyed with congo-red, under white light.
B. Dyed with congo-red under polarized light revealing apple-green birefringence, indicating amyloidosis.



Risk Profile	Treatment
Low-risk Patient Eligible for Autologous Stem Cell Transplantation	melphalan (HDM) and ASCT followed +/- bortezomib based therapy
High-risk Patients and Patients Ineligible for ASCT	bortezomib, bortezomib, cyclophosphamide and dexamethasone (CyBorD)
	bortezomib, melphalan, dexamethasone (BMDex)
	Oral melphalan + dexamethasone (if neuropathy, and t(11;14) translocation)
	Carfilzomib

this diagnosis less likely in our patient. However, considering the clinical presentation and rapid progression of the patient's nephrotic syndrome, kidney and liver failure, amyloidosis should be strongly suspected.

Amyloid Light Chain Amyloidosis (AL) and Amyloid A (AA) are the most common types encountered in clinical practice.[2,3] AA amyloidosis is commonly associated with chronic inflammatory diseases, resulting in amyloid A protein accumulation in tissues.[3] Contrarywise, in AL amyloidosis, the light chain immunoglobulins are deposited in target organs such as the liver, kidney, and heart.[3]

The heart, kidney, and liver are the three most common organs affected by amyloidosis. Hepatic amyloid commonly presents with nonspecific symptoms of fatigue and weight loss.[4] In cases of hepatic amyloidosis, more than 80% of the patients present with proteinuria and elevated ALP.[4,5] As seen in our case, peripheral blood smear findings suggesting hypersplenism are also common in patients with hepatic amyloidosis. Imaging can include diffuse or focal decrease in hepatic parenchymal attenuation and triangular-shaped hepatomegaly.[5] Although hepatic involvement is encountered in about 90% of patients with AL amyloidosis, progression to acute liver failure is highly rare.[6]

2. Which test needs to be done next to confirm the diagnosis (and exclude others)?

In patients with suspected liver amyloidosis, prompt diagnosis is crucial since hepatic amyloidosis carries a poor prognosis. Among patients with primary hepatic amyloidosis, the median survival is 8-9 months without treatment.[8] Although amyloidosis can be diagnosed with less invasive methods, in cases where the diagnosis is unclear and the differential remains broad, a liver biopsy should be performed. Characteristic histopathologic finding for liver amyloidosis is congo red staining of tissue demonstrating apple-green birefringence under polarized light.[7] (Figure 1)

Further evaluation with immunofixation, kappa lambda ratio, cardiac assessment with troponins, B-type natriuretic peptide, and cardiac imaging to rule out cardiac amyloid involvement should also be performed in every patient with a new diagnosis of amyloidosis.[2]

In our case, the patient received both a liver and kidney biopsy, which showed AL amyloidosis. In addition, bloodwork showed a significantly elevated kappa lambda ratio without evidence of cardiac disease.

3. What are the treatment options for the patient's condition?

Amyloidosis is a devastating disease, and no cure exists yet. Current treatment options focus on symptomatic improvement and prolonging survival. The most successful treatment approach to date involves induction therapy followed by high dose melphalan (HDM) and Autologous Stem Cell Transplantation (ASCT) at institutions specializing in amyloidosis.[7] Unfortunately, only 15% to 20% of patients are eligible to undergo this intensive therapeutic pathway owing to a high risk of treatment-related mortality.[7] An alternative, highly effective regimen for newly diagnosed amyloidosis includes the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD).[2,7] A summary of the available treatment options is outlined in Table 1.

Our patient declined transfer to a tertiary

institution with amyloidosis specialization, so she was started immediately on CyBorD. Given her combined liver and renal failure, her prognosis was poor. The patient had worsening hypotension and encephalopathy, and a family discussion with Palliative Care decided to proceed to hospice care. The patient passed away within a month of her hospital admission and within four months since her first laboratory abnormalities and leg edema development.

CONCLUSION

Primary hepatic amyloidosis is a rare disease but an important one for a clinician to recognize. Hepatic amyloidosis should be suspected in cases of hepatomegaly, elevated ALP, and proteinuria, especially after ruling out other common liver diseases. Liver biopsy remains the gold standard for diagnosing amyloidosis. The treatment option for non-ASCT transplant candidates is chemotherapy. Overall, while the prognosis is poor, <12 months, and worse with concomitant renal or cardiac involvement, a prompt diagnosis may help prolong survival. ■

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