Subacute Liver Failure Secondary to Amyloid Light-Chain Amyloidosis

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Case Report

A previously healthy 50-year-old man presented to his primary care physician with fatigue. Screening blood tests revealed a bilirubin level of 14 µmol/L (0.82 mg/dL), an aspartate aminotransferase (AST) level of 57 IU/L, an alkaline phosphatase (ALP) level of 72 IU/L, a γ-glutamyl-transpeptidase level of 126 IU/L, an albumin level of 30 g/L, and hypercholesterolemia. Results from hepatitis B and C viral serology testing and a liver autoantibody panel were negative. Dipstick urinalysis revealed proteinuria, and the patient's protein creatinine ratio was significantly elevated (950 mg/mmol; normal, <45 mg/mmol). The patient was referred to a nephrologist and underwent a renal biopsy, which demonstrated an expansion of the mesangial matrix by eosinophilic, hypocellular material. The arterial and arteriolar walls, glomeruli, Bowman capsule, and renal interstitium were positive when stained with Congo red (Figure 1). These findings were consistent with amyloid light-chain (AL) amyloidosis.

In order to stage the amyloidosis, the patient underwent ^{123}I-labeled serum amyloid P (SAP) scintigraphy. This procedure revealed a moderate-to-large amyloid load with involvement of the kidneys, liver, and spleen (Figure 2). An echocardiogram did not show significant cardiac dysfunction. A bone marrow trephine demonstrated an excess of plasma cells, and myeloma was diagnosed. Therefore, a chemotherapy regimen of bortezomib (Velcade, Millennium Pharmaceuticals), cyclophosphamide, and dexamethasone was scheduled.

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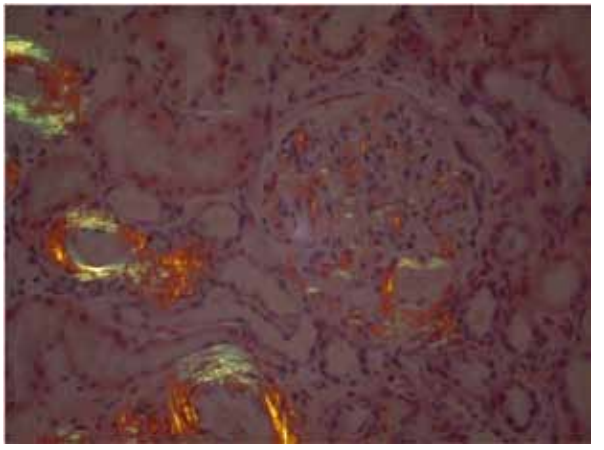

Figure 1. A renal biopsy showing apple-green staining of the arterial and arteriolar walls, glomeruli, Bowman capsule, and interstitium (Congo red stain, 20× magnification).

Image courtesy of Dr. Nicholas Marley, Consultant Pathologist, Queen Alexandra Hospital, Portsmouth, United Kingdom.

Unfortunately, prior to commencing chemotherapy, the patient's condition deteriorated, with progressive weight loss and the development of dyspnea. A physical examination revealed hepatomegaly, abdominal distension, and gross peripheral edema; no other peripheral signs of chronic liver disease were seen. Repeat blood testing showed a significant deterioration in liver biochemistry, with a bilirubin level of 48 µmol/L (2.81 mg/dL), an AST level of 72 IU/L, an ALP level of 1,121 IU/L, and an albumin level of 13 g/L; in addition, severe acute kidney injury was seen (Figure 3). A computed tomography (CT) scan confirmed hepatomegaly with patent hepatic and portal veins and no biliary dilatation. A large volume of ascites was also seen (Figure 4).

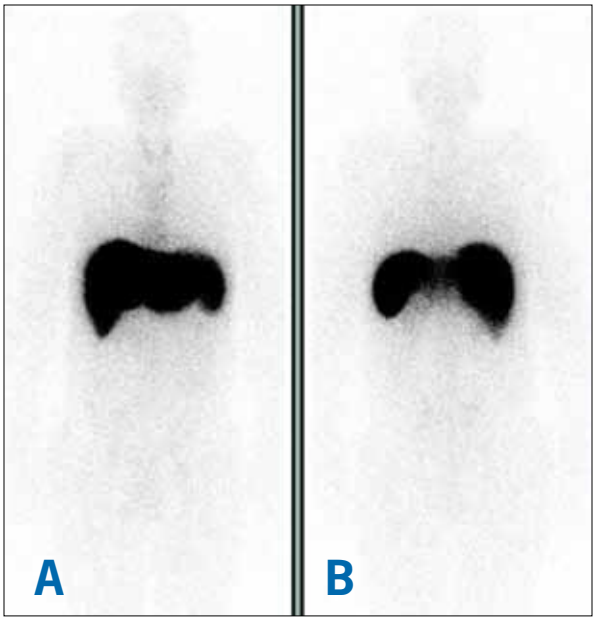

Figure 2. Anterior **(A)** and posterior **(B)** views of ^{123}I-labeled serum amyloid P scintigraphy demonstrating amyloid deposition in the liver and spleen.

Image courtesy of the Amyloid Centre, Royal Free Hospital, London, United Kingdom.

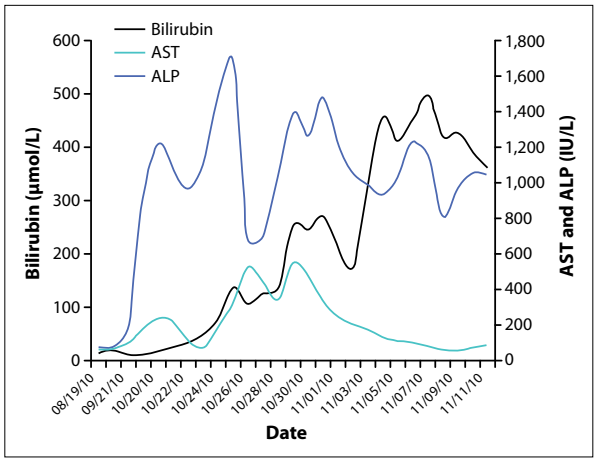

Figure 3. Results of the patient's liver biochemistry tests.

ALP=alkaline phosphatase; AST=aspartate aminotransferase.

The patient was prescribed cyclophosphamide, dexamethasone, and co-trimoxazole, and he awaited healthcare funding approval for bortezomib. His renal failure was treated with hemodialysis. Two days later, the patient's level of consciousness deteriorated to 7 out of 15 on the Glasgow Coma Scale. He was admitted to the intensive care unit for airway protection and mechanical ventilation. The findings of a CT brain scan were normal. The patient's coma was thought to be secondary to a combination of uremia and hepatic encephalopathy. The patient's synthetic liver function worsened, and his international normalized ratio reached 3. Chemotherapy was suspended due to concerns that it may have contributed to the patient's rapid decline in liver function.

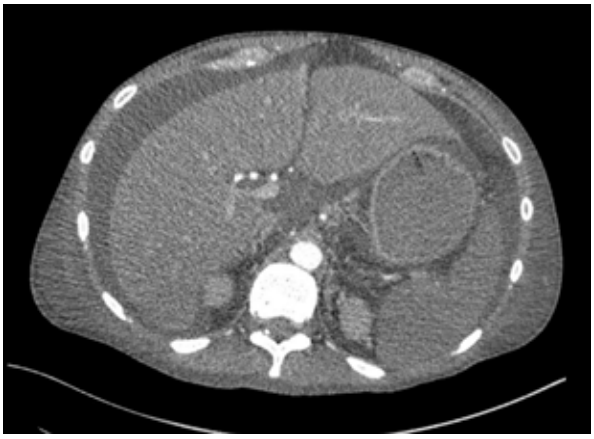

Figure 4. An abdominal computed tomography scan demonstrating hepatosplenomegaly and ascites.

The patient's case was discussed with the regional center for liver transplantation. Unfortunately, the patient was not considered to be a suitable candidate because of his multiorgan failure, progressive amyloidosis, and underlying malignancy. He continued to be managed in the intensive care unit with mechanical ventilation, hemofiltration, vasopressors, nasogastric feeding, laxatives, and broad-spectrum antibiotics. Although his renal function began to improve and he was extubated, his liver function test results continued to deteriorate. One week later, the patient died, just 3 months after the appearance of his presenting symptoms and 2 months after the development of jaundice.

Discussion

Systemic AL amyloidosis has an age-adjusted incidence of 5.1–12.8 cases per million person-years in the United States.[1] This condition is characterized by progressive extracellular deposition of insoluble fibrils derived from κ or λ immunoglobulin light chains within various organs. AL amyloidosis is classified as either primary amyloidosis (85%) or myeloma-associated amyloidosis (15%).[2] Organs commonly infiltrated include the kidneys and heart.[3] Although hepatic deposition occurs in half of cases, it is usually clinically silent, and the liver is rarely the dominant organ.[4,5]

Gertz and Kyle examined 80 patients with biopsy-confirmed hepatic amyloidosis and reported that 8% had a bilirubin level above 30 µmol/L (1.72 mg/dL), and 4%

had a bilirubin level exceeding 100 µmol/L (5.75 mg/dL).[5] Frank jaundice is rare in AL amyloidosis, with a prevalence of approximately 5%.[6] Signs of portal hypertension, including splenomegaly and ascites, are also infrequently reported in hepatic amyloidosis, with prevalences of 5% and 10–20%, respectively.[5,7,8]

However, closer examination of the literature reveals a cohort of patients who develop rapidly progressive intrahepatic cholestasis as a result of hepatic amyloid deposition. Liu and associates performed a literature review of 33 patients with AL amyloidosis and associated severe intrahepatic cholestasis.[9] The median patient age was 61 years, and men were more commonly affected than women (23 men vs 10 women). The most common presenting features were massive hepatomegaly (85%), ascites (58%), pruritus (41%), splenomegaly (29%), and gastrointestinal bleeding (18.5%). Peters and coworkers presented 5 cases of AL amyloidosis and examined an additional 20 cases from the literature.[6] They found lethargy and abdominal pain to be common presenting symptoms and noted that massive hepatomegaly was present in nearly all of the cases (92%).

Liver function test results are usually normal or mildly elevated in patients with hepatic amyloidosis.[5] In patients with acute hepatic failure, the biochemical pattern was cholestatic in all published cases, with a median bilirubin level of 265 µmol/L (15.2 mg/dL) and a median ALP level of 1,132 IU/L.[9,10] The elevated bilirubin level was predominantly of direct type in nearly all cases.[10]

The pathogenesis of cholestasis in these patients remains unknown. It has been hypothesized that amyloid may be directly toxic to cholangiocytes or that heavy deposits of amyloid fibrils disrupt bile flow through intrahepatic and extrahepatic ducts.[9-11] However, a review of 28 histologic specimens in which hepatic amyloidosis was associated with an elevated bilirubin level revealed normal extrahepatic ducts throughout.[10] There have also been many documented cases of patients with extensive hepatic amyloid deposition who did not develop jaundice or a significantly elevated ALP level.[6] In these cases, ultrasonography or cross-sectional imaging should be performed to rule out coexisting biliary obstruction.

Another abnormal finding documented in patients with amyloid-associated severe intrahepatic cholestasis is thrombocytosis, which is thought to be the result of functional hyposplenism.[6] In addition, hypercholesterolemia, as described above, has been reported in 2 other cases; interestingly, 1 patient went on to receive a liver transplantation, after which his cholestasis resolved, although his lipid status remained unchanged.[12,13]

The most commonly used diagnostic test for AL amyloidosis is immunofixation of serum or urine to detect a monoclonal light chain, although a liver biopsy may be required to confirm the diagnosis. There have been concerns that amyloid infiltration results in vascular fragility and, thus, an increased risk of hemorrhage following biopsy.[14] However, Park and colleagues reviewed 98 patients with hepatic amyloidosis and reported only 4 cases of bleeding following liver biopsy, none of which were associated with hepatic rupture or death.[15] The overall incidence of hemorrhage following liver biopsy for suspected hepatic amyloidosis is approximately 5%.[4] Common histopathologic findings include profound infiltration of the liver parenchyma leading to atrophy of hepatocytes as a result of increased sinusoidal pressure.[10]

Another important diagnostic modality is SAP scintigraphy. Radiolabeled SAP can be used as a tracer to detect the extent and distribution of deposits in both amyloid-associated and AL amyloidosis.[16] In addition to providing information regarding the extent of the spread of amyloidosis, the distribution pattern may give an indication of the particular fibril type. There is a good correlation between hepatic uptake in SAP scintigraphy and deranged liver function.[16]

No effective treatment has been established for hepatic amyloidosis.[17] No benefit was demonstrated in early studies examining prednisolone and colchicine (either separately or in combination); a combination of cyclophosphamide, prednisolone, and melphalan; or dimethylsulfoxide.[6,18] A more recent trial of high-dose melphalan and autologous stem cell transplantation in systemic AL amyloidosis showed improvement in two thirds of patients with hepatic disease.[19] An additional study reported a positive outcome in patients without extrahepatic involvement who were treated with bone marrow transplantation following liver transplantation.[20]

In our patient, the combination of bortezomib and dexamethasone was considered. This regimen is a well-established treatment option for myeloma and has recently been examined in patients with AL amyloidosis (although not in patients with hepatic involvement).[21] The overall response rate in patients with systemic AL amyloidosis was 54%, with 31% of patients achieving complete hematologic remission. The median response time was 7.5 weeks. Overall mean survival was 18.7 months, although this duration had not yet been reached in all patients who achieved complete remission.

There are some concerns regarding the use of bortezomib in the setting of chronic liver disease due to this drug's hepatic metabolism; for this reason, our patient did not receive this drug. The manufacturers of bortezomib advise dose reduction in patients with moderate or severe liver dysfunction.[22] However, a recent review suggested that bortezomib should be avoided in patients with severe hepatic impairment.[23]

Unfortunately, the prognosis for patients with AL amyloidosis and hepatic involvement remains generally poor. A recent review of 28 patients with AL amyloidosis and hepatic involvement reported a mean survival of 3 months, in contrast to an overall survival of 20 months for patients with AL amyloidosis alone.[10,24] A literature review of 80 patients reported a median survival of 1.8 months once bilirubin levels reached 25.7 µmol/L (1.5 mg/dL).[5] When AL amyloidosis was associated with severe intrahepatic cholestasis, the most common causes of death were renal failure (42%) followed by combined hepatorenal failure (21%).[9]

Summary

AL amyloidosis is an uncommon disorder leading to infiltration of several organs, with renal and cardiac involvement usually having the most clinical significance. Although hepatic involvement commonly occurs, it usually does not affect prognosis. However, our patient was an example of a patient with hepatic amyloidosis who developed a syndrome of rapidly progressive intrahepatic cholestasis associated with massive hepatomegaly and features of portal hypertension, including splenomegaly, ascites, and varices. Prompt recognition of this presentation is vital, and the use of SAP scintigraphy to view infiltrated organs is of great value, in combination with histopathologic confirmation of the diagnosis. The prognosis of these patients is grave without prompt chemotherapy or transplantation, which may not be possible if the condition is not promptly recognized. Therefore, the possibility of hepatic amyloidosis should be carefully considered by clinicians in cases of cholestatic jaundice without an apparent cause.

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Review

Amyloidosis and Subacute Liver Failure

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Acute liver failure (ALF) is a rare disorder defined by the clinical progression of jaundice to hepatic encephalopathy in the absence of preexisting liver disease in fewer than

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Table 1. King's College Hospital Criteria for Emergency Liver Transplantation

ALF caused by acetaminophen (paracetamol)
pH <7.3 (irrespective of hepatic encephalopathy grade)

OR all of the following criteria:

- PT >100 sec
- Hepatic encephalopathy grade >3
- Creatinine level >300 μmol/L

ALF caused by nonacetaminophen (nonparacetamol)
PT >100 sec (irrespective of hepatic encephalopathy grade)

OR any 3 of the following criteria:

- Age <10 years or >40 years
- Bilirubin level >300 μmol/L
- PT >50 sec
- Non-A and non-B hepatitis of unfavorable etiology, halothane hepatitis, idiosyncratic drug reactions
- Duration of jaundice prior to hepatic encephalopathy >7 days

ALF=acute liver failure; PT=prothrombin time.

28 days. Subacute liver failure (SALF) is defined as the occurrence of this progression in 28–72 days.[1] SALF, which is rare, is associated with seronegative hepatitis, drug-induced liver failure, autoimmune hepatitis, Budd-Chiari syndrome, and Wilson disease.[2] Once the criteria for poor prognosis have been met, the only effective treatment for this condition is emergency liver transplantation (ELT). The 1-year survival rate for patients who do not receive ELT is 10–15%, compared to approximately 79% for patients who do receive ELT.[3] Patient selection for ELT is most commonly determined by the King's College Hospital criteria.[4] These criteria differ based on the cause of the ALF: acetaminophen (paracetamol) or non-acetaminophen (nonparacetamol; Table 1). The cardinal features of SALF are jaundice, hepatic encephalopathy, and coagulopathy. Malignant processes causing ALF have been previously described but are uncommon.[5]

The case reported by Hydes and Aspinall involves a 50-year-old man who presented to his primary care physician with fatigue.[6] The main abnormality identified at this consultation was proteinuria. Due to this condition, the patient was referred to a nephrologist and underwent a renal biopsy, which led to the diagnosis of amyloid light-chain (AL) amyloidosis. Prior to the commencement of chemotherapy, the patient's condition worsened. At this time, findings from the patient's liver function tests were noted to be abnormal. The patient had jaundice, and his serum alkaline phosphatase (ALP) level was significantly elevated. In the absence of biliary obstruction, a high ALP level is associated with primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced liver injury, infiltrative processes (including sarcoidosis), lymphoma, and tumors (primary or secondary). If there is significant bone involvement, the presence of multiple myeloma may also have an impact on ALP level. It would be interesting to know the patient's γ-glutamyltranspeptidase level at this time.

The patient's abdominal pain and hepatomegaly prompted consideration of Budd-Chiari syndrome. The presence of heavy proteinuria may lead to deficiency in anticoagulant factors, including anti-thrombin III, protein C, and protein S. Although Budd-Chiari syndrome has been described in the presence of myeloma, it was not the diagnosis in this patient.[7]

The patient's liver function test results continued to worsen; at this point, perhaps liver tissue could have been obtained to secure a histologic diagnosis. At the time of presentation, the patient's aspartate aminotransferase level was elevated (57 IU/mL). The authors do not disclose information that may have been pertinent to this elevation, particularly the patient's alcohol history and risk factors for fatty liver disease or other metabolic liver diseases. It is conceivable that the patient may have had underlying liver cirrhosis and may have suffered an acute-on-chronic decompensation precipitated by alcohol, drug ingestion, or sepsis in addition to the AL amyloidosis. The presence of heavy amyloid deposition on serum amyloid P scintigraphy likely ushered the clinical team away from a liver biopsy (LB). In the past, there have been concerns of an increased bleeding risk from percutaneous LB in patients with amyloidosis, although this risk may have been overstated; nevertheless, the bleeding risk in these patients remains higher than for other LB indications.[8,9] If there were concerns regarding this risk, a transjugular LB could have been performed, particularly because of the patient's worsening coagulopathy.[10] A LB may have identified cirrhosis (thereby excluding ELT) and could have demonstrated hepatic amyloidosis and hepatic necrosis (as a consequence of SALF).

A LB may also have identified hepatic monoclonal plasma cell infiltration of myeloma. This condition has been reported in up to 40% of cases and responds to corticosteroids.[11-14] The King's College Hospital Acute Liver Failure Group described a case of hepatic amyloidosis secondary to myeloma that led to SALF without hepatomegaly in the presence of a normal serum ALP level, a negative test result for bence jones protein (a protein that is positive in 20% of cases), and a normal erythrocyte sedimentation rate. In this case, the presence of amyloidosis and myeloma was only determined from liver and bone marrow histologic examination on autopsy, highlighting the importance of histology.[15] Hepatic failure is an unusual consequence of myeloma-associated AL amyloidosis.[15-17] SALF is even rarer in amyloid-associated

amyloidosis. Only a small number of such cases have been reported in the English language medical literature.[18-20]

In the setting of ALF or SALF, the occurrence of acute renal failure is an ominous sign. According to O'Grady's criteria for poor prognostic factors in ALF, severe renal impairment and metabolic acidosis behold a poor outcome in the absence of ELT.[4] Other possibilities for acute renal failure in this situation include dehydration, sepsis, drug-induced nephrotoxicity, myeloma kidney, nephrotic syndrome, and possibly hepatorenal syndrome (if the patient is cirrhotic).

Transfer to the intensive care unit and the subsequent need for intubation, broad-spectrum antibiotics, and vasopressors herald the onset of multiple organ failure (MOF). Outcomes for patients with MOF are abysmal in the setting of ALF and cirrhosis.[21,22] It has been postulated that sepsis often serves as the catalyst for clinical deterioration and MOF.[23] Prophylactic antibiotics and antifungal agents are routinely prescribed for the management of patients with ALF syndromes. This practice appears to reduce the risk of infection, but it does not necessarily influence overall survival.[24,25]

Multiple myeloma is the second most common hematologic malignancy (13%) and constitutes 1% of all cancers. Primary amyloidosis arises from diseases with disordered immune cell function, such as multiple myeloma and other immunocyte dyscrasias. AL amyloidosis is the most common form of systemic amyloidosis. It occurs in 5–15% of individuals with multiple myeloma. Liver involvement is less common in myeloma (32%) than in other hematologic malignancies: 80–100% in chronic leukemia and myeloproliferative diseases, 60–70% in acute leukemia, and 50–60% in non-Hodgkin lymphoma. As in the case reported by Hydes and Aspinall, these patients often present with hepatomegaly, jaundice, and ascites; fulminant liver failure per se is rare.[6,26,27] The presence of intrahepatic cholestatic jaundice is considered to be a bad prognostic sign, as is the presence of ascites.[28,29] It should be noted that ascites is a feature of SALF and is not unique to cirrhosis in liver disease, although this distinction is difficult to discern via imaging alone.

A recently published series of all AL amyloidosis patients evaluated at the UK National Amyloidosis Centre who underwent liver transplantation between 1984 and 2009 reported 1-year and 5-year survival rates of 33% and 22%, respectively. These figures do not meet the minimum survival rate required to justify liver transplantation as a viable treatment modality (ie, a 50% chance of survival 5 years post–liver transplantation).[30] Nevertheless, there have been case reports of AL amyloidosis patients doing well with sequential liver and stem cell transplantations.[31-34] Therefore, liver transplantation may be indicated as a life-saving procedure in well-selected cases of rapidly progressing hepatic amyloidosis.

In summary, the interesting case reported by Hydes and Aspinall describes a rare cause of SALF attributed to AL amyloidosis.[6] This case shows that ascites and features of portal hypertension do not develop only in the setting of decompensated cirrhotic liver disease but also in more acute settings. Failure to recognize these findings may prevent some patients from gaining access to life-saving ELT. The outlook for patients who undergo transplantation for AL amyloidosis is poor compared to other indications, but prolonged survival may be possible in well-selected cases. Finally, this case highlights the potential role of LB in the setting of SALF.

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