CASE REPORT

Acute liver failure due to primary amyloidosis in a nephrotic syndrome: a swiftly progressive course

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SUMMARY

AL amyloidosis is a clonal plasma cell proliferative disorder characterised by extracellular tissue deposits of insoluble fibrils derived from κ or λ immunoglobulin light chains. The most common organs affected by AL amyloidosis are the kidney, presenting with nephrotic syndrome and/or progressive renal dysfunction, and the heart, with restrictive cardiomyopathy. Hepatic deposition of fibrils occurs in half the cases but the liver is rarely the predominantly affected organ. The most common presentation of hepatic amyloidosis is hepatomegaly with elevated alkaline phosphatase. Acute liver failure with cholestasis and jaundice is a rare complication, with a prevalence of approximately 5%, and is usually associated with a worse prognosis. We report a case of a 39-year-old man admitted to our nephrology department with an unusual presentation of primary amyloidosis with nephrotic syndrome and acute liver failure, complicated by obstructive cholestasis resulting in death 2 months after diagnosis.

BACKGROUND

AL amyloidosis, previously referred to as primary amyloidosis, results from extracellular tissue deposition of fibril-forming monoclonal immunoglobulin (Ig) light chains (LC), most commonly of λ isotype, secreted by a clone of plasma cells (PC) in the bone marrow.^{1–3} This rare disorder leads to infiltration of several organs, with the kidney and heart being the most affected, with typical manifestations such as nephrotic syndrome and restrictive cardiomyopathy, respectively. Peripheral neuropathy and hepatomegaly with elevated liver enzyme levels are also common, but usually do not affect prognosis. The Ig free LC (FLC) level at diagnosis,⁴ the number of involved organs⁵ and the serum uric acid level,⁶ have been associated with prognosis. The exact incidence is unknown, but in the USA, there are approximately 6–10 cases per million person-years, with a male predominance.⁷ The average age at diagnosis is 65 years, and <10% of patients are under the age of 50 years.¹ We report an unusual case of primary amyloidosis in a 39-year-old man, presenting with nephrotic syndrome and rapidly progressive intrahepatic cholestasis, associated with hepatomegaly and features of portal hypertension. There are few reported cases in the literature of acute liver failure as a manifestation of AL amyloidosis. The present case highlights liver failure due hepatic amyloid deposition as a contributor to poor prognosis.

CASE PRESENTATION

A 39-year-old Caucasian man was admitted to our hospital, with progressive asthenia, muscle weakness, dizziness, generalised oedema and abdominal distension, for the past 2 months. He also referred a weight loss of 10 kg over the past year. He denied fever, jaundice, abdominal pain, vomiting, diarrhoea, constipation, gastrointestinal bleeding and other symptoms. His medical history included hypertension, controlled with amlodipine 5 mg per day, and prior surgery for achalasia, 2 years before. He referred moderate alcohol intake for >10 years (100 g/week).

His physical examination revealed hypotension (blood pressure 90/40 mm Hg), periorbital and marked lower limb oedema, and abdominal palpation was remarkable for a firm, non-tender liver palpated 5 cm beneath the right costal margin. No purpura, no petechiae and no ecchymoses were observed.

Laboratory results at admission were as follows: haemoglobin 19.2 g/dL (normal range (NR) 12.5–17.0 g/dL) with haematocrit 55.8% (NR 40–50%) and white cell count $11.5 \times 10^9/L$ (NR 3.8– $10.5 \times 10^9/L$), with normal platelets. Prothrombin and partial thromboplastin time were increased, 30.1 seg (NR 12.0–17.4 seg) and 39.5 seg (NR 25–34 seg), respectively. The patient's renal function was preserved (serum creatinine (sCr) 0.95 mg/dL, NR 0.72–1.18 mg/dL), but he presented with severe hypoalbuminaemia of 1.9 g/dL (NR 3.5–5.2 g/dL), dyslipidaemia with total cholesterol 509 mg/dL (low-density lipoprotein cholesterol 353 mg/dL), and triglycerides 492 mg/dL and high uric acid of 9.3 mg/dL (NR 3.5–7.2 mg/dL). Regarding hepatic cholestasis and cytolyses enzymes, aspartate aminotransferase was 90 U/L (NR <35 U/L), alanine aminotransferase 39 U/L (NR <45 U/L), alkaline phosphatase 938 U/L (NR 40–150 U/L) and γ -glutamyl transpeptidase 1254 U/L (NR <55 U/L) with normal bilirubin 0.5 mg/dL (NR, 0.3–1.2 mg/dL). C reactive protein was slightly increased (0.94 mg/dL; NR <0.05 ng/dL). The spot urine protein-to-creatinine ratio was 10 010 mg/g. We performed a renal ultrasound, which was normal, but abdominal ultrasound revealed hepatomegaly and splenomegaly of 15 cm. Chest radiography showed an increased cardiothoracic index.

On the basis of the patient's clinical symptoms together with laboratory data showing proteinuria, hypoalbuminaemia and hyperlipidaemia, he was admitted to our nephrology department with the diagnosis of nephrotic syndrome.

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Additional testing revealed a high level of κ -FLC of 73.9 mg/L (NR 6.70–22.4) and high ratio FLC κ/λ 3.08 (NR 0.31–1.58) with normal levels of the remaining Ig. Serum protein electrophoresis and serum immunofixation were negative for gammopathy, but urinary 24 h immunofixation revealed a monoclonal peak of κ -FLC. C3 and C4 levels, rheumatoid factor, antistreptolysin titre, antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins and glomerular basement membrane antibodies, were within the reference values. Autoimmune profile was negative for hepatitis, α -fetoprotein was within normal limits and serologies for hepatitis A, B, C, E and HIV were negative. Investigation for the JAK2 V617F mutation was also performed, since the patient had polyglobulia, and it was negative.

Owing to the patient's altered coagulation profile, percutaneous renal biopsy was contraindicated, so a transjugular liver biopsy was ultimately performed with the patient's consent. Six portal spaces were visualised. A loss of lobular organisation due to deposition of perisinusoidal eosinophilic amorphous material was present (figure 1), conditioning some areas of trabecular collapse and hepatocanalicular cholestasis (figure 2). This material had an affinity for periodic acid-Schiff and stained with Congo red (figure 2), exhibiting apple-green birefringence with polarised light. Immunohistochemistry staining was positive for serum amyloid P and κ -LC. Stains for serum amyloid A and λ -LC were negative. The histopathological diagnosis was a κ -LC amyloidosis. Bone marrow aspirate cytology showed 1.6% PC, and immunophenotyping detected two populations of these cells, 28% were phenotypically normal, with the remaining 72% positive for CD 38, CD 138, CD 56 CD 27 and presenting intracytoplasmic κ -LC. Metastatic skeletal radiological assessment was negative. ECG showed left ventricular hypertrophy voltage criteria, but echocardiogram did not show significant cardiac dysfunction, with a left ventricular ejection fraction of 59%. Electromyography showed compression of the median nerve within the carpal, with sensorimotor stage advanced peripheral nerve conduction velocities.

Consequently, a chemotherapy regime of cyclophosphamide and dexamethasone was started, while the patient awaited healthcare funding approval for bortezomib. He was discharged after 2 months of admission in stable clinical condition, with sCr 0.9 mg/dL.

OUTCOME AND FOLLOW-UP

One week after discharge, the patient was readmitted for a rapidly degrading condition with progressive weight loss,

Figure 1 H&E (magnification $\times 100$)—loss of lobular organisation owing to the deposition of perisinusoidal eosinophilic amorphous material.

Figure 2 Congo red (magnification $\times 200$)—extracellular deposition of Congo red-positive amorphous proteinaceous material. Loss of lobular organisation owing to the deposition of perisinusoidal eosinophilic amorphous material, conditioning areas of trabecular collapse and hepatocanalicular cholestasis.

muscular wasting and refractory hypotension. He presented with dyspnoea, jaundice and Acute Kidney Injury Network (AKIN) stage 3 acute kidney injury (AKI), with a sCr of 5.6 mg/dL and oliguria requiring haemodialysis. Biochemistry results showed a significant deterioration in liver function, with bilirubin level of 7.8 mg/dL (direct bilirubin of 6.0 mg/dL), aspartate aminotransferase 90 U/L, alanine aminotransferase 70 U/L, alkaline phosphatase 1715 U/L, γ -glutamyl transpeptidase 2014 U/L and albumin 1.5 g/dL. Coagulation test showed a prothrombin time of 70.1 seg and partial thromboplastin time of 43.5 seg. An ultrasound confirmed hepatomegaly with biliary dilation and large volume ascites. The patient was not considered to be a suitable candidate for transplant due to multiorgan failure, and he died 1 week later, just 2 months after the appearance of his presenting symptoms.

DISCUSSION

We reported a case of a patient with AL amyloidosis, whose primary manifestation was acute liver failure and nephrotic syndrome. AL amyloidosis presenting with acute liver failure is a rare manifestation. At the Mayo Clinic, of 229 patients with primary amyloidosis who were studied, hepatomegaly and a modestly raised alkaline phosphatase were present in 34% and 16%, respectively, and the presence of hyperbilirubinaemia was seen in only 4%.⁸ Similar to the case described, the most common presenting symptoms were fatigue and weight loss, seen in 54% and 42%, respectively.⁹

Regarding the medical history (moderate alcohol consumption), laboratory (cholestasis) and instrumental data (hepatomegaly and splenomegaly), the differential diagnosis of its underlying cause was challenging and included primary biliary cirrhosis (PBC), PBC-autoimmune hepatitis and hepatocellular carcinoma. Regarding the nephrotic syndrome, nephropathy associated with HIV was immediately ruled out, as was lupus nephritis. The most commonly used diagnostic test for AL amyloidosis is immunofixation of serum or urine to detect a monoclonal LC, but in approximately 10% of patients, it is impossible with routine immunofixation techniques.^{8 10} In our case, urinary immunofixation revealed the monoclonal peak of κ -LC proteinuria, which is a hallmark of AL amyloidosis. However, λ -LC is the most frequent LC found in AL amyloidosis, and is also more associated with nephrotic proteinuria.¹¹

This patient developed AL amyloidosis at a younger age than expected, as studies have reported ages at diagnosis below 40 years in only 5% of cases.^{8 9}

AL amyloidosis can also occur in patients with other PC dyscrasias, including multiple myeloma, malignant disorders of PC or lymphoplasmacytic cells. The main differential diagnosis is in a patient with proteinuria and a monoclonal component is multiple myeloma, which is associated with AL amyloidosis in approximately 10% of cases. Multiple myeloma such as AL amyloidosis is most frequently diagnosed at an advanced age. However, the young age of the patient, the absence of anaemia, hypercalcaemia and lytic bone lesions, as well as <30% PC in the bone marrow, allowed exclusion of the presence of multiple myeloma.

Renal biopsy is considered essential by some authors, since the kidney is involved in virtually all cases, and most often presents as asymptomatic proteinuria or nephrotic syndrome in 50% of cases. In our patient, renal impairment manifested initially by nephrotic proteinuria and later with renal insufficiency, which led to hospital readmission. The progression to end-stage renal disease is known, despite therapy.

Contrary to what happens in patients with multiple myeloma, AKI is rare in AL amyloidosis.¹² It can be related with hypoperfusion, acute tubular necrosis, acute tubulointerstitial nephritis or renal vein thrombosis. It can also develop from a rapid deposit of fibrils in the glomerulus, tubules and vessels.¹³ The management of patients with AKI associated with PC dyscrasia is to start immediate chemotherapy to decrease LC production, correct volume depletion and avoid nephrotoxic drugs; extracorporeal techniques, such as plasmapheresis, can be effective to remove excessive LC.¹⁴

Since kidney biopsy was contraindicated in our patient, due to haemorrhagic diathesis, we performed a transjugular liver biopsy, which still remains the definitive method of detecting liver involvement in amyloidosis. As in other cases with clinically unsuspected primary amyloidosis,¹⁵ the diagnosis was made by liver biopsy. Bleeding diathesis may occur, due to factor X deficiency (amyloid fibrils binding in the liver and spleen), a decrease of vitamin K-dependent clotting factors, increased antithrombin activity fibrinolysis and intravascular coagulation. However, the overall incidence of haemorrhage following liver biopsy for suspected liver amyloidosis is approximately 5%.¹⁶

The diagnostic of polycythaemia vera was also ruled out by negative JAK2 V617F mutation, and erythrocytosis was presumed to be secondary to high altitude. Moreover, gastrointestinal involvement is less common, with clinically apparent disease occurring in only 1%. In retrospect, this patient's history of achalasia 2 years earlier might resemble an early manifestation of amyloidosis AL, since gastrointestinal manifestations include gastroparesis, bleeding, constipation, bacterial overgrowth, malabsorption and intestinal pseudo-obstruction resulting from dysmotility.¹⁷

Since this patient was in the fourth decade of life and showed a good performance status without major findings on echocardiogram (interventricular septum 13 mm, with an ejection fraction of 59%, without multiple myeloma and a sCr<2 mg/dL), he was considered to be eligible for intensive treatment.

The combination of bortezomib with cyclophosphamide and dexamethasone (CyBorD) was considered in our patient. This is the treatment with which our institution has more experience, and it is the best studied in the literature. It has demonstrated rapid responses in a majority of patients with AL amyloidosis and, in recent studies, the overall haematological response rate in patients with AL amyloidosis to CyBorD ranges from 60% to

81%, with renal responses of 25%.^{18 19} Unfortunately, the availability of bortezomib is limited and healthcare funding approval for it can take up to 3 weeks. Owing to his rapid progression to acute hepatic failure with cholestasis, the patient was not eligible for autologous stem cell transplantation.

Cyclophosphamide therapy is associated with minor transient serum enzyme elevations and has been linked with rare cases of acute injury. The onset of liver injury is within 2–8 weeks of starting cyclophosphamide and the pattern of serum enzyme elevations is hepatocellular.²⁰ When given in high doses as a part of myeloablative therapy in combination with total body irradiation or busulfan, in preparation for haematopoietic cell transplantation, it can cause acute sinusoidal obstruction syndrome.²¹ In our case, acute liver failure seems to be related to the primary disease, regarding the abnormalities on laboratory, imaging and histological findings present prior the administration of cyclophosphamide. Also, the cholestasis pattern is not so typical and acute liver failure is usually related to the association with total body irradiation.

Amyloidosis is a rare entity that is difficult to diagnose. However, AL amyloidosis should be seriously considered in any adult with non-diabetic nephrotic syndrome having other signs or symptoms such as non-ischaemic cardiomyopathy with 'hypertrophy' on echocardiography; hepatomegaly without imaging abnormalities of the liver; demyelinating polyneuropathy; or the presence of a monoclonal gammopathy in a patient with unexplained fatigue, oedema or weight loss.²²

Unfortunately, the prognosis for patients with AL amyloidosis and hepatic involvement remains poor, and some studies have reported a mean survival of 3 months when hepatic involvement is present, in contrast to an overall survival of 20 months for patients with AL amyloidosis without hepatic involvement.^{23 24} In patients with bilirubin levels higher than 1.5 mg/dL, median survival of 1.8 months has been reported.²⁵ In the presence of severe cholestasis, the most common causes of death are renal failure followed by combined hepatorenal failure.²³

Learning points

- ▶ Finding a paraprotein is the diagnostic hallmark of AL amyloidosis.
- ▶ All patients with nephrotic syndrome should have immunofixation of serum and urine as part of their initial evaluation.
- ▶ Infiltrative diseases such amyloidosis must be considered when a patient presents non-specific symptoms with abnormal liver function tests.
- ▶ A liver biopsy is essential for the diagnosis of primary amyloidosis when liver enzyme abnormalities dominate the initial clinical picture.
- ▶ Liver involvement in patients with amyloidosis is often an indicator of poor prognosis.

Contributors BAC was responsible for data collection, literature review, writing of the manuscript and leadership, and submitted the manuscript for publication. RL wrote the manuscript and contributed to the literature review. HS and MC provided the intellectual concept.

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