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Single Case

Massive Hepatomegaly Secondary to Amyloidosis with Normal Liver Chemistries

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Amyloidosis · Liver · Hepatomegaly · Congo red staining

Abstract
Amyloid light chain (AL) amyloidosis is a disease of misfolded, fibrous proteins, either kappa or lambda subtype, that can be deposited into one or more organs, caused by a proliferation of plasma cells. The liver is uncommonly the main organ system affected and rarely the only organ affected by amyloid deposition. With hepatic involvement, the most common presenting findings are hepatomegaly and elevation of serum alkaline phosphatase. We report a case of a 50-year-old male who presented to our gastroenterology clinic with marked hepatomegaly secondary to hepatic amyloidosis, in concert with bone marrow involvement and nephrotic syndrome. Biopsies in conjunction with Congo red staining demonstrated 95% replacement of hepatic structure and 80% replacement of bone marrow with amyloid deposition. Despite these findings, liver chemistries, renal function, and blood count were normal. Our case presents not only the rare finding of primary hepatic amyloidosis but also an atypical presentation of this disorder. Although rare, AL amyloidosis should be in a differential diagnosis of any patient who presents with unexplained hepatomegaly, nephrotic-range proteinuria, heart failure with preserved ejection fraction, fatigue, weight loss or a history of monoclonal gammopathy of undetermined significance.

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Introduction

Amyloidosis encompasses a rare group of disorders resulting from extracellular deposition of amyloid proteins in one or more organs. Amyloid deposits consist of aggregates of insoluble, fibril-forming proteins [1]. Progressive accumulation of amyloid can disrupt tissue architecture and lead to organ dysfunction and in severe cases life-threatening organ failure [2].

Amyloid light chain (AL) amyloidosis, previously referred to as primary amyloidosis, represents the most common type of systemic amyloidosis. It occurs as the result of an overproduction of clonal immunoglobulin light chains in patients with monoclonal proliferation of plasma cells or other B-cell lymphoproliferative disorder [2]. Most patients affected by AL amyloidosis are over the age of 50, and the prevalence and incidence are higher in males than in females. It occurs in approximately 10–15% of all patients with multiple myeloma [3, 4]. The heart is the organ most commonly involved in AL amyloidosis (71% of the patients) [5]. Other organs and systems frequently affected include the kidney, peripheral nervous system, and gastrointestinal tract [3, 5].

Hepatic involvement in AL amyloidosis is common, although it is rarely the only organ affected by amyloid deposition. When the liver is involved, amyloid is deposited within the space of Disse along the hepatic sinusoids or within the walls of hepatic blood vessels [6]. The clinical manifestations of hepatic amyloidosis are usually mild and frequently include hepatomegaly, and elevated serum alkaline phosphatase and other liver chemistries [6, 7]. In rare cases, portal hypertension, hepatic rupture, or hepatorenal failure are seen [7–9]. Here, we present an unusual case of primary hepatic amyloidosis involving a patient with hepatomegaly and nephrotic syndrome, yet with normal liver chemistries and renal function.

Case Presentation

A 50-year-old Caucasian male, with a history of obesity, type 2 diabetes mellitus controlled with metformin and insulin, and reflux esophagitis treated with omeprazole, was referred to our clinic with constant right upper-quadrant fullness discomfort, with an 18-kg weight loss over the preceding 4 years, including a 4.5-kg weight loss in the last month. Transaminases had fluctuated up to 2 times normal in the preceding 20 years. A liver biopsy performed 15 years previously revealed hepatic steatosis with moderate inflammatory infiltrate, foci of piecemeal necrosis, and fibrosis without bridging. At presentation, the patient described early satiety, nausea, orthostatic dizziness, chronic cough, and muscle atrophy. He denied chest pain, dyspnea, palpitations, or urinary symptoms. Family history was positive for diabetes mellitus and colorectal cancer without liver disease or amyloidosis. The patient denied a history of alcohol use or exposure risk factors for viral hepatitis. Marked hepatomegaly, predominantly of the left lobe, was seen on a computed tomography scan without other abnormality (Fig. 1). Recent colonoscopy demonstrated a diminutive hyperplastic polyp.

On physical examination, blood pressure was 110/66, weight 79.8 kg, and BMI 27.4. Prominent capillaries were noted in the upper anterior chest, and the cardiac examination was unremarkable. The left hepatic lobe was palpable 7 cm below the xiphoid without splenomegaly, discernible ascites, or pedal edema. Laboratory values included albumin 3.6 gm/dL, alkaline phosphatase 85 IU/L, ALT 14 IU/L, AST 24 IU/L, total bilirubin 0.57 mg/dL, total protein 6.8 gm/dL, BUN 9.8 mg/dL, creatinine 0.73 mg/dL, glucose 96 mg/dL, platelet count 371,000, MCV 89, and HbA1C 5.7.

Twenty-four-hour urine showed total protein 6.3 g; urine immunofixation demonstrated a faint amount of monoclonal free lambda light chain, and serum protein electrophoresis demonstrated an acute inflammatory pattern. Serum immunofixation did not detect monoclonal proteins. APTT, INR, CK, HBsAg, HCV Ab, AFP, TTG IgA, and total IgA were normal or negative. Nerve conduction studies in his upper extremities were normal. Echocardiogram was nonspecific. Liver biopsy revealed parenchyma infiltrated with amorphous, eosinophilic, globular deposits involving 95% of the specimen, mainly in the sinusoids with rare intact hepatocytes, and portal fibrosis (Fig. 2). A Congo red stain revealed congophilic material with green birefringence under polarized light, confirming amyloid consisting of lambda immunoglobulin light chains (Fig. 2). No steatosis was identified, and the parenchyma was negative for iron. The kappa/lambda ratio was elevated at 34 mg/L (normal to 26.3). Serum beta 2 microglobulin, IgA, and IgG were normal, with mildly decreased IgM. Subsequent bone marrow biopsy revealed 80% of the space occupied by amyloid, confirmed by Congo red stain (Fig. 3). Blasts were not increased, and storage iron was decreased. Lambda light chain restricted plasma cell population was detected by immunohistochemistry and flow cytometry, representing 10–20% of overall cellularity. The monoclonal plasma cells expressed CD 138, CD 38, CD 10, and CD 56. A concurrent complete blood count was normal with absence of rouleaux formation. Cytogenetic analysis showed a normal male karyotype in all cells analyzed.

The patient was treated with chemotherapy consisting of bortezomib, cyclophosphamide, and dexamethasone for 6 months, and developed peripheral neuropathy. Repeat bone marrow biopsy performed 7 months after treatment cessation demonstrated a decrease in the number of lambda light chain restricted plasma cells to 3–5% of cellularity. At this point, amyloid deposits represented 20–40% of the marrow space. A third bone marrow biopsy performed 6 months later revealed plasma cell burden to be approximately 5–10%, with <1% lambda light chain restricted; however, amyloid material occupied 60–80% of the marrow space.

Discussion

AL amyloidosis is rare, with an incidence of 10–15 patients per million per year in the United States [4]. The clinical manifestations vary greatly depending upon organ involvement, which can make rapid diagnosis difficult. Heart failure with preserved ejection fraction is a frequent manifestation, occurring in approximately 70–80% of the cases; however, nonspecific findings on the echocardiogram make it difficult to use as a diagnostic feature [5]. Hepatic involvement frequently presents with hepatomegaly and abnormal liver function chemistries [7] and is often accompanied by nephrotic syndrome (defined as proteinuria >3.5 g/24 h and hypoalbuminemia), orthostatic hypotension, or peripheral neuropathy at diagnosis [6, 10].

Although liver involvement is not unusual in AL amyloidosis, it is particularly rare as the main organ affected [6]. Our case of hepatic amyloidosis is noteworthy in a number of ways. Despite 95% replacement of hepatic structure with amyloid deposition, our patient's liver function chemistries were completely normal at the time of diagnosis. This included normal alkaline phosphatase, which typically is significantly elevated in AL amyloidosis [7]. Coagulation factor levels were also normal, along with albumin, creatinine, and blood urea nitrogen levels, despite concurrent nephrotic syndrome. Lastly, his blood count was normal despite the presence of a significant amount of amyloid in the bone marrow.

The most common initial diagnostic test for AL amyloidosis is immunofixation of serum or urine to detect a monoclonal light chain immunoglobulin. Definitive diagnosis, however,

requires histological demonstration of amyloid. Fat pad aspiration [11] or salivary gland biopsy [12] are useful methods, although the sensitivity of these methods may fail to demonstrate amyloid deposits, in which case organ-specific biopsies might be required [2]. In our patient, urine immunofixation demonstrated a faint lambda free light chain. Proteinuria, another characteristic finding in AL amyloidosis, was also present. Since disorders other than AL amyloidosis may also result in nephrotic-range proteinuria with lambda free light chain in urine [13], liver biopsy was performed to confirm the diagnosis. The preferred method of liver biopsy in cases of suspected AL amyloidosis is a transjugular approach [10]. Bleeding complications following liver biopsy for suspected amyloidosis have been reported; however, the overall incidence rate is reported to be approximately 5% [7].

The primary treatment strategy for AL amyloidosis utilizes chemotherapy with the goal of targeting the underlying plasma cell or B-cell clone. Current treatment utilizes a proteasome inhibitor, typically bortezomib, in combination with alkylating agents (melphalan or cyclophosphamide) and dexamethasone [5]. Approximately 25% of patients with AL amyloidosis meet the eligibility requirements for autologous stem cell transplantation, which is often combined with chemotherapy [2, 5]. Our patient was treated with bortezomib, cyclophosphamide and dexamethasone without autologous stem cell transplantation, a regime reported to produce a 40% response rate when the liver is the primary organ involved [2]. Today, efforts to either inhibit amyloid formation or promote its disruption have met with limited success [5].

Prognosis of AL amyloidosis depends on the organ systems affected but is often poor when the heart is involved. The median survival of AL amyloidosis complicated by severe cardiac myopathy is <1 year [3]. Factors such as hyperbilirubinemia and increased number of plasma cells are associated with shorter overall survival. In patients with primary hepatic amyloidosis, the median survival is reported to be <1 year [7, 10]. These poor outcomes may be attributed in part to delayed diagnosis and therapy. Data gathered by the Amyloid Research Consortium indicate that 37% of the patients are diagnosed 1 year after the onset of initial symptoms and typically with advanced disease [14]. If AL amyloidosis is left untreated, it can culminate in rapid hepatorenal failure. When AL amyloidosis is treated, the amount of residual clonally abnormal plasma cells is considered the primary indicator of treatment response, rather than the residual amyloid which can vary from sample to sample [15].

Today, our patient is stable 2 years after cessation of chemotherapy, with residual lambda plasma cell burden of <1% of the cells, compared to 10–20% of the cells seen in the initial bone marrow biopsy. Factors that may have contributed to better prognosis in this case include the liver as the main organ affected, no cardiac involvement, and normal liver and renal function.

In conclusion, AL amyloidosis may manifest in a wide spectrum of presentations, including organ-specific disease, such as primary hepatic amyloidosis described in this patient. Although AL amyloidosis is rare and the signs and symptoms are often nonspecific, it should be on the differential diagnosis of any patient who presents with unexplained hepatomegaly, nephrotic-range proteinuria, heart failure with preserved ejection fraction, fatigue, weight loss or a history of monoclonal gammopathy of undetermined significance.

Statement of Ethics

Informed consent to publish this work was obtained from the patient. The name of the patient is not mentioned in this report nor is any other protected health information (PHI).

The University of Idaho Institutional Review Board (IRB) reviewed this case report and determined that IRB approval is not required for publication.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.J.H. served as the attending doctor for the patient. All authors made substantial contributions to analysis and interpretation of data and drafting and revising the manuscript. All authors approved the final draft to be submitted.

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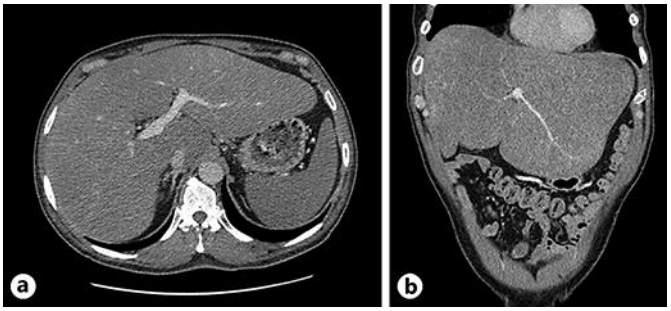

Fig. 1. Gross hepatomegaly as demonstrated by computed tomography. Axial scan (**a**) and coronal scan (**b**) of the abdomen displaying a significantly enlarged liver.

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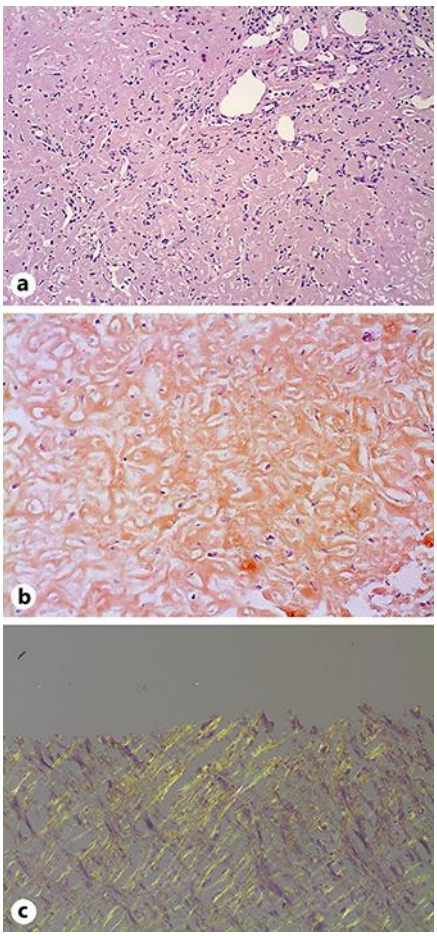

Fig. 2. Extracellular deposition of amyloid material in the liver. **a** Loss of hepatic lobular organization due to extensive deposits of amyloid, visible as eosinophilic amorphous material. HE. ×100. **b** Extensive deposits of amyloid visible as Congo red-positive amorphous proteinaceous material. Congo red, original magnification ×200. **c** Amyloid material demonstrating characteristic apple-green birefringence under polarizing light microscopy. Original magnification ×200.

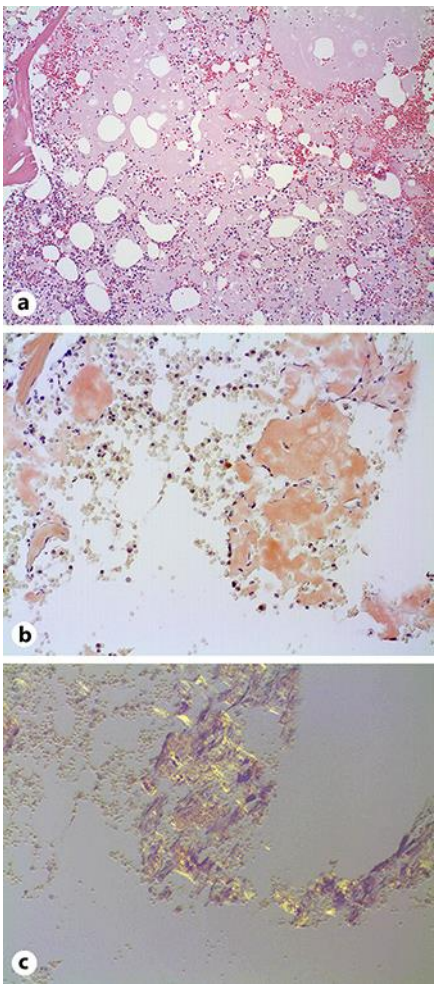

Fig. 3. Amyloid deposition in bone marrow. **a** Majority of bone marrow space occupied by amyloid deposits, visible as eosinophilic amorphous material. HE. ×100. **b** Amyloid within bone marrow space visible as Congo red-positive amorphous proteinaceous material. Congo red, original magnification ×200. **c** Amyloid material demonstrating characteristic apple-green birefringence under polarizing light microscopy. Original magnification ×200.