

Severe Obstructive Cholestasis and Hypercalcemia Caused by Light-Chain Amyloidosis: A Case Report

Zahra Davoudi¹, MD; Farahnaz Bidari², MD; Elena Jamali², MD; Shahriar Nikpour¹, MD

¹Department of Internal Medicine, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;

²Department of Pathology, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence:

Shahriar Nikpour, MD; Loghman Hakim Medical Center, Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, South Kargar St., Makhsus Ave., Postal Code: 13336-31151, Tehran, Iran

Tel: +98 9123386507

Fax: +98 21 88025105

Email: nikpour@sbmu.ac.ir

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What's Known

- Hepatic amyloidosis is a rare disease associated with a poor prognosis.
- The clinical manifestations of hepatic amyloidosis can be nonspecific and can lead to liver failure in severe cases.
- A correct diagnosis of hepatic amyloidosis is based on a liver biopsy.

What's New

- We reported on an unusual case of hepatic amyloidosis in a 57-year-old man, who initially presented with severe intrahepatic cholestasis and hypercalcemic crisis.
- The diagnosis of amyloidosis was based on a liver biopsy.

Abstract

Gastrointestinal amyloidosis is a condition caused by the deposition of extracellular protein fragments. It can be associated with complex and diverse pathways and can have numerous manifestations and etiologies. Hepatic amyloid light-chain (AL) amyloidosis is a rare disorder characterized by the deposition of the insoluble amyloid protein in the liver. The clinical presentations of AL amyloidosis are frequently non-specific. In this case report, we describe a patient with amyloidosis, who initially presented with an unusual case of severe intrahepatic cholestasis, which followed a rapidly progressive clinical course that was associated with the acute hypercalcemic crisis. The diagnosis of amyloidosis was made after the liver and bone biopsies were performed. Our findings revealed that AL amyloidosis should be considered, when a patient presents with cholestatic hepatitis, renal failure, and hypercalcemia.

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Keywords • Liver failure • Multiple myeloma • Amyloidosis

Introduction

Amyloidosis is a condition in which insoluble extracellular protein fragments are deposited into the serum. The amyloid protein accumulates in different tissues, leading to structural and functional disruptions.¹

Amyloid light-chain (AL) amyloidosis is the most prevalent type of systemic amyloidosis. It results from monoclonal gammopathy, causing abnormal levels of immunoglobulin (Ig) light-chain proteins to be deposited in the affected tissues, such as peripheral nerves, kidneys, and heart, and the liver can also be involved.²

Hepatic AL amyloidosis is a rare disease that presents with varying clinical symptoms, from the enlargement of the liver and abnormal liver function tests to hepatic failure, portal hypertension, and rarely, spontaneous rupture.³ The severity and prognosis of AL amyloidosis depend on the type and extent of organ involvement and early diagnosis and treatment.⁴

Herein, we describe an unusual case of AL amyloidosis in a 57-year-old man. He initially presented with rapidly progressive cholestasis associated with hypercalcemia.

Case Presentation

In January 2020, a 57-year-old man with hypertension, chronic

kidney disease, and hypothyroidism presented to the emergency department of Loghman Hakim Hospital in Tehran, Iran. He was admitted to the Hospital with anorexia, nausea, abdominal pain, generalized fatigue, and jaundice. He had also experienced an unintentional weight loss of 22 kg over two weeks. A physical examination revealed that he was in a state of confusion, and had generalized jaundice, hepatomegaly, and lower extremity edema. Written informed consent was obtained from the patient.

Table 1 column (a) represents the results of the initial laboratory tests. The symptoms suggested that the patient had a hypercalcemic crisis. The relevant treatment was administered, consisting of intravenous saline, furosemide, calcitonin, denosumab, and one-time hemodialysis.

The markedly elevated levels of alkaline phosphatase (ALP) and the total and direct bilirubin levels supported the diagnosis of hepatic cholestasis. The patient had no history of fever, renal stones, or fractures, and no significant risk factors for hepatic disorders. Further investigations were performed to assess the etiology of the low levels of parathyroid hormone (PTH) in the serum. Generally, low levels of PTH signify the presence of non-parathyroid hypercalcemia, which should prompt a detailed investigation for malignancy or other causes of the disease, including sarcoidosis or granulomatous diseases, such as tuberculosis. In addition, the levels of angiotensin-converting enzyme (ACE) were determined, urine and

serum immunoelectrophoresis were performed and a chest radiograph and computed tomography (CT) scans of the lung and abdomen were carried out. It should be noted that a PTH-related protein (PTHrP) test was not performed, since it was not available. The results of the ACE level analysis were negative.

Upon consultation with a gastroenterologist, an upper gastrointestinal (GI) endoscopy was performed, revealing no specific abnormalities. An ultrasound and CT of the abdomen demonstrated that the liver was enlarged. Magnetic resonance cholangiopancreatography (MRCP) was employed to rule out any obstructions, strictures, or malignancies. MRCP revealed that there were no special abnormalities in the biliary system.

Subsequent investigations included measurements of the Epstein–Barr virus (EBV) antibody, anti-cytomegalovirus (CMV) antibody, anti-smooth muscle antibody, anti-liver kidney microsome, human immunodeficiency virus (HIV) antibody, acute viral hepatitis A, B, and C antibodies, antinuclear antibody (ANA), and anti-mitochondrial antibody (AMA). Direct and indirect Coombs tests and the Wright test were also performed.

To determine the diagnosis, a liver biopsy was carried out. The histopathologic findings shed light on the fragmented liver tissue with diffuse perisinusoidal deposits of homogenous eosinophilic hyaline material and compression atrophy of hepatocyte plates. Congo red-stained

Table 1: The initial (a) and subsequent (b) results of the laboratory investigations

Variable	Initial results (a)	Subsequent results (b)	Normal range
White cell count	12.60 k/uL	15 k/uL	4-10
Hemoglobin	11 g/dL	10 g/dL	12-16
Platelet count	394 k/uL	450 k/uL	150-450
Blood urea nitrogen	40 mg/dL	120 mg/dL	8-23
Creatinine	2.60mg/dL	2.90 mg/dL	0.7-1.3
Aspartate transaminase	60 U/L	158 U/L	14-35
Alanine transaminase	34 U/L	120 U/L	15-35
Alkaline phosphatase	2526 U/L	2800 U/L	38-126
Total bilirubin	8.30 mg/dL	22.70 mg/dL	0.1-1.2
Direct bilirubin	5.80 mg/dL	17.80 mg/dL	< 0.3
Partial thromboplastintime	35 s	40 s	22-35
Prothrombin time	13.50 s	16 s	12-14.5
International normalized ratio	1.30	1.60	0.8-1.2
Calcium	16.20 mg/dL	10.50 mg/dL	8.5-10.5
Albumin	3.50 g/dL	3 g/dL	3.5-5
Phosphate	2.60 mg/dL	2.70 mg/dL	2.5-4.5
Gamma-glutamyltransferase	-	81 IU/L	11-50
25-hydroxyvitamin D ₃	-	27 ng/mL	20-50
Parathyroid hormone	-	11 pg/mL	10-65
24-hour urine calcium	-	108 mg/24L	100-300
24-hour urine protein	-	1680 mg/24L	20-150
Thyroid-stimulating hormone	1.20 mu/L	-	0.4-4.5

sections demonstrated typical apple-green birefringence under polarized light, confirming the diagnosis of hepatic amyloidosis. An immunohistochemical (IHC) analysis revealed kappa light chain immunoreactivity, although the lambda light chain and amyloid A were negative (figure 1).

The patient's chest radiograph and CT scan were normal. Moreover, serum protein electrophoresis (SPE) did not show the presence of monoclonal gammopathy. Urine protein electrophoresis (UPE) revealed the presence of mixed tubular and glomerular proteinuria.

Due to the patient's history of chronic renal failure and proteinuria and the clinical presentations of hypercalcemia and hepatic amyloidosis, the most common background pathogenicity was gammopathy and multiple myeloma (MM). Although the SPE and UPE did not indicate any evidence of monoclonal gammopathy, a bone marrow biopsy demonstrated hypercellular bone marrow for age with a few patchy deposits of amyloid protein and no increase in the population of plasma cells. Subsequent IHC staining of the bone marrow for lambda and kappa light chains implied the deposition of monoclonal (kappa) light chains, compatible with the results shown in the liver (figure 2). The clinical presentations of hypercalcemia, renal failure, and hepatic cholestasis combined with the results of the paraclinical investigations (liver and bone marrow

biopsies) confirmed a diagnosis of systemic AL amyloidosis and hepatic amyloidosis.

The patient was referred to an oncologist for his progressive symptoms. He was a candidate to be treated with dexamethasone and lenalidomide, which are prescribed for AL amyloidosis. However, the patient refused the treatment. His clinical condition worsened due to the progressive increase of liver enzymes, leading to liver failure. The patient expired four months after the initial diagnosis.

Discussion

In this report, we described a patient, who had AL amyloidosis and an initial presentation of severe intrahepatic cholestasis and hypercalcemia. It should be noted that treatment is the first step in managing acute and severe hypercalcemia. Clinical findings strongly suggested non-parathyroid hypercalcemia, indicating the need to search for an underlying malignancy.⁵

Patients with gastrointestinal amyloidosis often present with non-specific symptoms of fatigue, weight loss, hepatomegaly, and elevated ALP levels.³ Our patient presented with weight loss, hepatomegaly, jaundice, and elevated ALP levels. The highlighted symptoms were the dysfunction of the hepatic and biliary systems, caused by the deposition of an amyloid protein precursor in the hepatic tissue, and hypercalcemia, which resulted from

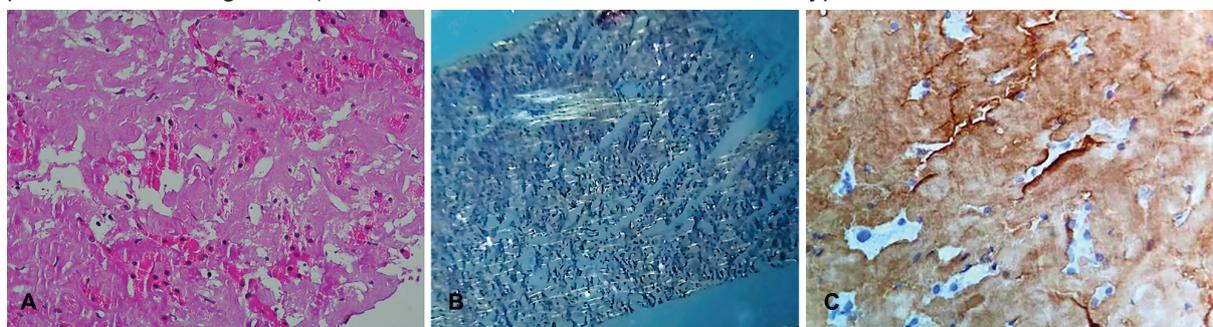


Figure 1: Liver biopsy sections show hepatic amyloidosis. (A) The section illustrates a diffuse deposit of amorphous eosinophilic amyloid replacing the liver parenchyma and a few remaining scattered hepatocytes (H&E stain; 400 \times). (B) Apple green birefringence under polarized light (Congo red stain; 400 \times). (C) Immunoreactivity of the kappa light chain (IHC stain; 400 \times).

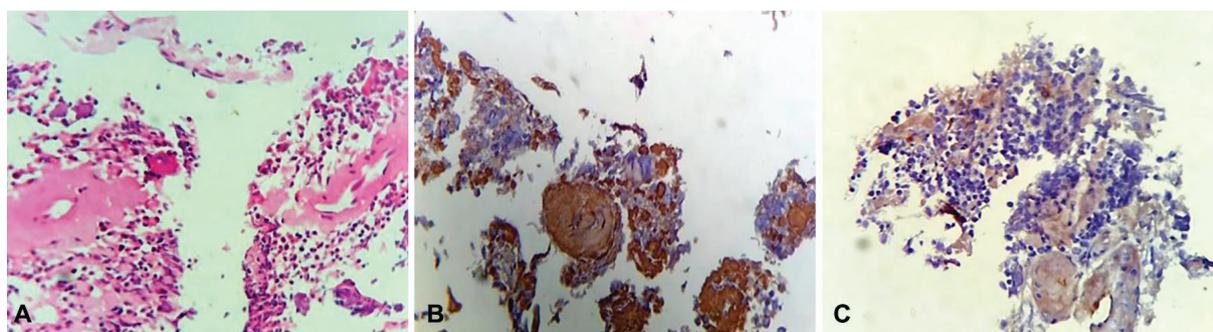


Figure 2: Bone marrow biopsy sections. (A) Patchy amyloid protein deposits are depicted in the vessel walls and the marrow. (B) The kappa light chain restriction with IHC staining. (C) The IHC staining of the lambda light chain is negative.

gammopathy and the clonal proliferation of Ig proteins in bone.

Liver involvement due to light-chain amyloidosis can be the first indication of MM. MM causes extreme abnormal bone remodeling, and over 80% of patients with MM have bone disease.⁶ In addition, 73% of patients present with anemia at diagnosis;⁷ on the other hand, the rest 30% have renal insufficiency and hypercalcemia.^{8,9}

Autopsies have shown that up to 96% of patients with AL amyloidosis have hepatic amyloidosis.¹⁰ AL amyloidosis is associated with a wide range of symptoms able to mimic other prevalent conditions. Therefore, the diagnosis of AL amyloidosis is often delayed. A prompt diagnosis and treatment of the disease require a tissue biopsy utilized to detect amyloid deposits.¹¹

Cross and others reported a 46-year-old woman, who had hepatic amyloidosis concurrently with MM and bone marrow involvement.¹² Yim and colleagues highlighted the poor outcomes and difficult management of two patients with hepatic amyloidosis.¹³ Both patients initially presented with abdominal pain, hepatomegaly, and elevated ALP levels, and died due to severe hepatic impairment.

The main parameters related to disease severity and prognosis are early detection and management of the disease along with the type and extent of the affected organs.^{4,14} Moreover, therapeutic strategies are based on the organ involved in amyloidosis and thus, are not the same. However, most patients are treated with chemotherapy or biological therapy.¹⁵ A randomized clinical trial (RCT) implied that patients with amyloidosis, who underwent chemotherapy had higher survival rates and showed clinical improvement compared with untreated individuals.⁸ In this case, our patient refused treatment with dexamethasone and lenalidomide, which are typically prescribed for AL amyloidosis.

The prognosis of patients with AL amyloidosis involving the liver is poor and the survival rate is less than two years. Elevated ALP levels can also predict a poor prognosis,⁴ which is in line with our findings. Thus, the rapid diagnosis and delivery of appropriate treatments may improve the poor outcomes of hepatic amyloidosis.

Conclusion

This case report highlighted several uncommon initial findings associated with AL amyloidosis, such as severe intrahepatic cholestasis and hypercalcemic crisis. Hepatic amyloid light-chain (AL) amyloidosis should be considered, when a

patient presents with cholestatic hepatitis, renal failure, and hypercalcemia.

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Conflict of Interest: None declared.

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