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A rare cause of painful hepatomegaly

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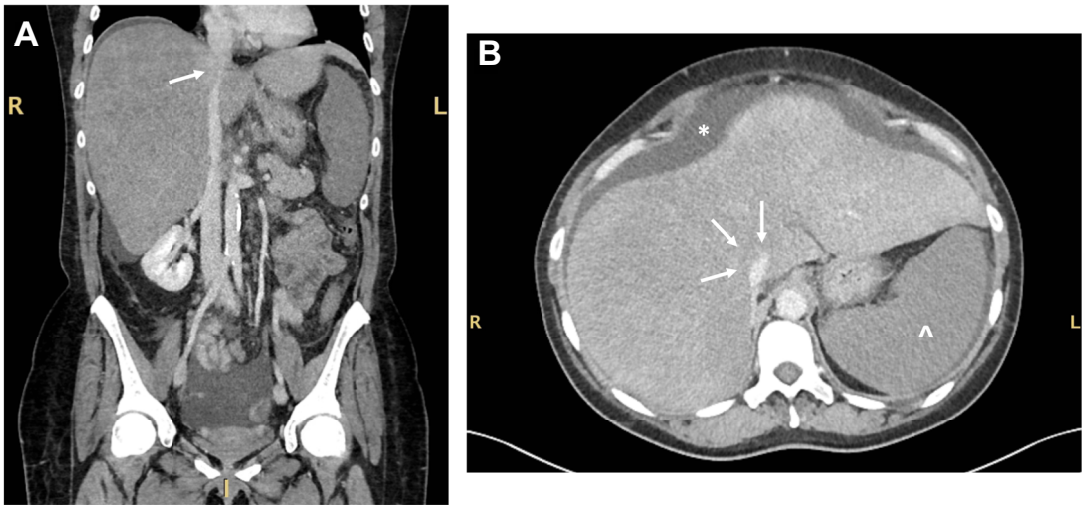

Fig. 1. Abdominal CT scan. The CT scan showed an enlarged, dysmorphic liver, compression of the retro-hepatic inferior vena cava (arrow, A), splenomegaly (^, B), and ascites (*, B); hepatic veins were abnormal, compressed by the liver parenchyma, and not clearly visible in the venous phase (arrows, B).

Description

A 50-year-old female was admitted to our inpatient service due to abdominal pain, nausea, and progressive fatigue. The symptoms started a few weeks before hospitalization when she was treated with oral antibiotics for a dental infection. Vitals were normal. Physical examination showed an enlarged liver and bilateral leg edema. Medical history included smoldering myeloma (diagnosed a few weeks before admission), autoimmune thyroiditis (since 2018), and Sjogren's syndrome (since 2020). Labs demonstrated leukocytosis ($15x10^9$/L, with an upper limit of normal [ULN] of $11x10^9$/L), normocytic anemia (hemoglobin 11 g/dl), normal platelet count, international normalized ratio of 1.5, normal bilirubin, slight elevation of aspartate aminotransferase (66 U/L; ULN: 45 U/L), normal alanine aminotransferase, significant increases in gamma-glutamyltransferase (241 U/L; ULN: 45 U/L) and alkaline phosphatase (ALP: 404 U/L; ULN: 214 U/L), and a modest increase in C-reactive protein (14 mg/L; ULN: 5 mg/L). Albumin was reduced (19 g/L); serum protein electrophoresis showed an increase in gamma globulin without a monoclonal component. Carcinoembryonic antigen, alpha-fetoprotein, and carbohydrate antigen 19-9 were normal; HBV, HCV, and HIV serology were negative. The CT scan showed a dysmorphic and enlarged liver (compressing the retro-hepatic inferior vena cava), splenomegaly, and ascites (Fig. 1A). Notably, the hepatic veins were not clearly visible in the venous phase, a finding that was confirmed by two independent radiologists with specific expertise in liver imaging (Fig. 1B). Based on the radiological findings and clinical suspicion of Budd-Chiari syndrome, we started anticoagulant treatment with low-molecular weight heparin. A week later, she underwent catheterization of the inferior vena cava and hepatic veins; surprisingly, all these veins were patent though the inferior vena cava was significantly compressed in the retro-hepatic tract; there was no spider web. A trans-jugular liver biopsy was performed.

What is your diagnosis?

1. DILI (drug-induced liver injury).
2. Autoimmune hepatitis.
3. Hepatic amyloidosis.
4. Small hepatic veins Budd-Chiari syndrome.

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Diagnosis and patient's outcome

The microscopic examination of the liver biopsy showed massive deposits of an amorphous, eosinophilic extracellular material, which was consistent with amyloid. As shown in Fig. 2, the amyloid completely replaced the normal liver parenchyma; there were only scattered, atrophic liver cell plates with few portal tracts left; hepatic sinusoids were completely obliterated.

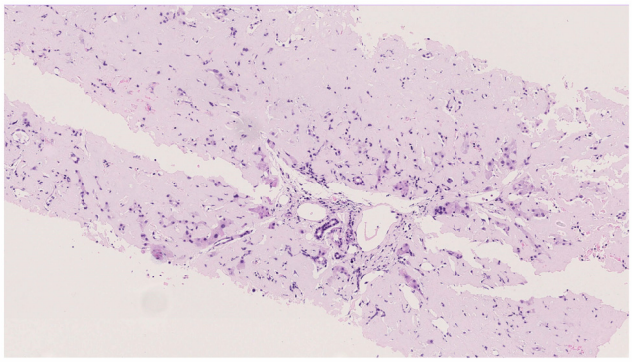

Fig. 2. Histologic images of the liver biopsy sample showing hepatic amyloidosis. The normal liver parenchyma was massively replaced by extensive deposits of an amorphous, eosinophilic, extracellular material, which was consistent with hepatic amyloidosis. Hematoxylin-eosin, 10×.

Hematologists recommended abdominal fat biopsy for further characterization of the hepatic amyloidosis. However, the abdominal fat biopsy was negative (fluorescence with thioflavin x100 is shown in Fig. 3A), a finding that was confirmed by electron microscopy (Fig. 3B).

We performed additional examinations of the liver biopsy (Fig. 4). Thioflavin stain at fluorescence revealed diffuse deposits of amyloid, completely substituting the liver parenchyma (Fig. 4A). Electron micrography (Fig. 4B) showed immunoreactivity for kappa light chain of amyloid fibrils, as demonstrated by a post-embedding immunogold method (kappa light chains, scale bar 1.0 μm).

These histopathological and electron micrography findings were consistent with the diagnosis of hepatic involvement in amyloid light-chain (AL) amyloidosis. The patient was therefore re-evaluated by hematologists and started chemotherapy with bortezomib, dexamethasone, and daratumumab.

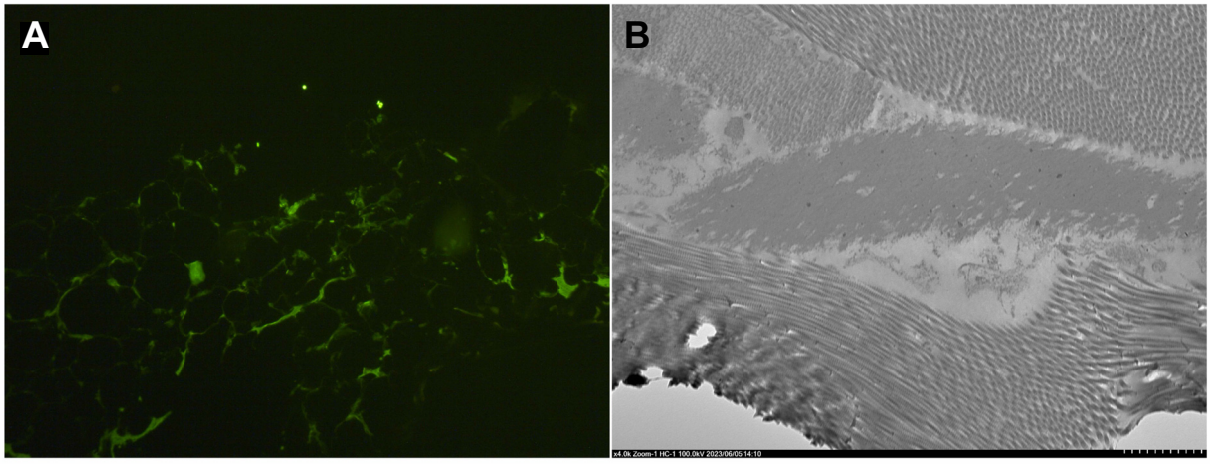

Fig. 3. Abdominal fat excisional biopsy. (A) Fluorescence was negative for amyloidosis (thioflavin 100×); (B) Electron micrograph showing normal collagen and elastic fibers (*i.e.,* no evidence of amyloidosis), as demonstrated also by a post-embedding immunogold method (kappa light chains, scale bar 2.0 μm).

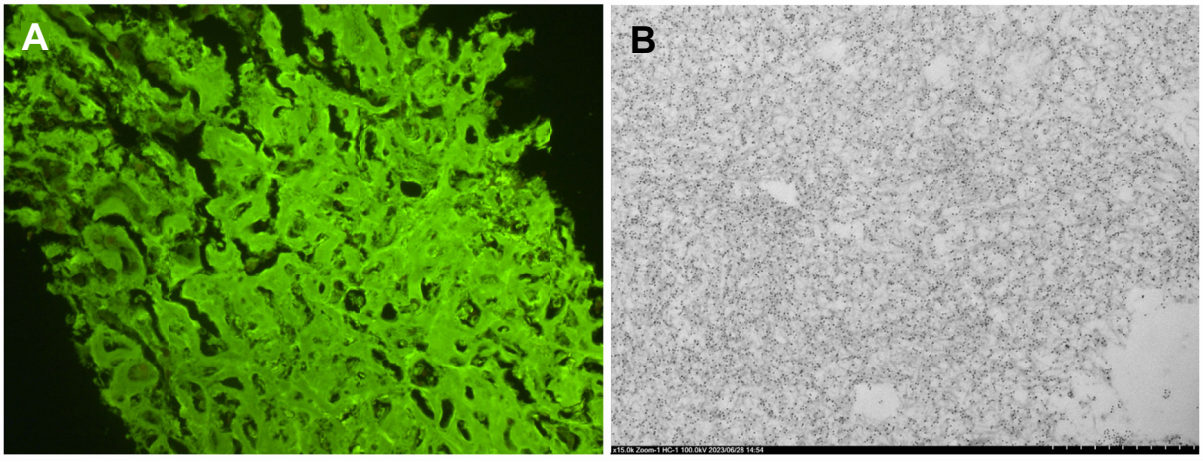

Fig. 4. Liver biopsy (fluorescence and electron micrography). (A) Fluorescence highlights diffuse amyloid deposits substituting liver parenchyma (thioflavin 100×); (B) Electron micrograph showing immunoreactivity for kappa light chain of amyloid fibrils, as demonstrated by a post-embedding immunogold method in keeping with light-chain amyloidosis (kappa light chains, scale bar 1.0 μm).

Hepatomegaly and sinusoidal portal hypertension in hepatic amyloidosis

AL amyloidosis, previously known as primary amyloidosis, is a rare disease resulting from extracellular deposition of amyloid. Amyloid consists of aggregates of insoluble, misfolded, fibril-forming proteins.[1] AL amyloidosis is caused by the overproduction of clonal immunoglobulin light chains, either kappa or lambda, in patients with monoclonal proliferation of plasma cells or other B-cell lymphoproliferative disorders.[1] In patients with multiple myeloma, the prevalence of AL amyloidosis is 10%–15%. This patient was evaluated by hematologists a few weeks before hospitalization due to progressive fatigue, anemia, and hepatosplenomegaly. The bone marrow biopsy – performed to exclude a myeloproliferative disease – showed a clonal proliferation of plasma cells, which was indicative of a multiple myeloma. Per the hematologist's assessment, however, there were "no clinical elements indicating that the plasma cell proliferation could be symptomatic", and the hepatosplenomegaly was ascribed to a primary hepatic cause such as cirrhosis.

AL amyloidosis is a systemic disease. The heart is the most commonly affected organ (70%-80% of patients), though the kidneys, peripheral nervous system, and gastrointestinal tract can be variously involved.[2] We performed echocardiogram and cardiac MRI, which excluded a restrictive cardiomyopathy; kidney function tests were normal with no proteinuria, and there were no signs or symptoms of neurologic involvement. Hepatic involvement in AL amyloidosis is frequent; in one autopsy study, the prevalence of histological alterations was ~70%.[3] Usually, amyloid is deposited within the space of Disse either along the sinusoids or within the walls of hepatic blood vessels.[3] Clinical manifestations of hepatic amyloidosis, which are observed in 20%–30% of patients, are generally mild; these mostly include hepatomegaly ± elevation in ALP.[1] More rarely, portal hypertension and its complications may occur.[1] Our case is noteworthy because the liver was the only significantly affected organ at diagnosis. As shown in Fig. 2, the hepatic parenchyma was almost completely substituted; notably, hepatic sinusoids were totally obliterated, thus explaining the obstructive syndrome with clinically significant portal hypertension and ascites.

Demonstration of amyloid deposition in a tissue biopsy by Congo red staining is the gold standard for diagnosis.[1] The most accessible site is periumbilical fat. Tissue deposits should be typed using mass spectrometry (the current gold standard), immunoelectron microscopy, or immunohistochemistry.[1] Understanding the fibril type is important because multiple proteins can cause systemic amyloidosis, each requiring specific therapy.

Target organs can be biopsied for either diagnosis or staging. In patients with suspected hepatic involvement, the transjugular route may be the safer method; moreover, it allows for the indirect assessment of sinusoidal pressure, which has prognostic value. In this patient, the hepatic venous pressure gradient was significantly increased (wedge hepatic vein pressure of 25 mmHg – free hepatic vein pressure of 4 mmHg = 21 mmHg). We also found a significant hemodynamic gradient between the inferior vena cava (19 mmHg) and the right atrium (2 mmHg), reflecting compression by the enlarged liver (Fig. 1A). In fact, the patient had significant bilateral leg edema despite no cardiac amyloidosis and correction of hypoalbuminemia. It bears noting that procedure-related bleeding after liver biopsy for suspected hepatic amyloidosis may occur; in a previous series from the Mayo Clinic, the incidence of bleeding following liver biopsy (any type) was 4%.[4]

In conclusion, AL amyloidosis may occur in a large variety of clinical presentations, including organ-specific diseases, such as the primary hepatic amyloidosis of this patient. Signs and symptoms of hepatic amyloidosis are not specific; however, we suggest that it should be considered in the differential diagnosis of any patient who presents with unexplained hepatomegaly, increased ALP, or signs of clinically significant portal hypertension, especially if they have a history of monoclonal proliferation of plasma cells or other B-cell lymphoproliferative disorders.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All the authors contributed to the conceptualization, writing and revision of the manuscript; AZ: final revision and approval.

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Supplementary data

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