Case Report

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Hepatic veno-occlusive disease may be a rare characteristic of hepatic involvement in systemic amyloidosis: case report and literature review

Tong-Yin Zhu[1,2,3], Guan-Hui Zhou[1,2,3], Xin-Hua Chen[1,2,3], Xiao-Dong Teng[4] and Jun-Hui Sun[1,2,3]

Abstract

Systemic amyloidosis is a rare disease and patients with hepatic amyloidosis often present with hepatomegaly. Hepatomegaly can also be a feature of hepatic veno-occlusive disease (HVOD). We report here a case of systemic amyloidosis in a patient who was suspected of having HVOD. On the basis of computed tomography findings in the abdomen, HVOD was initially suspected in a 63-year-old man with the chief complaint of upper abdominal pain, ascites, and weight loss. Multiple patchy purpura and nerve symptoms were identified and these were due to amyloidosis. An increase in proteinuria and immunoglobulin κ light-chain levels, and thickening of the ventricular wall supported the diagnosis of systemic light-chain amyloidosis involving the liver, heart, kidney, skin, and nerves. This diagnosis was confirmed by histological examination of a bone marrow core biopsy with Congo red dye. Sequential treatment of bortezomib and dexamethasone led to good results in the patient. Findings of this rare case indicate that HVOD can be diagnosed without a definite history of

[1]Hepatobiliary and Pancreatic Interventional Treatment Center, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[2]Key Laboratory of Combined Multi-organ Transplantation, Ministry of Public Health, Hangzhou, China
[3]Collaborative Innovation Center for Diagnosis Treatment of Infectious Diseases, Zhejiang University, Hangzhou, China
[4]Division of Pathology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Corresponding author:
Jun-Hui Sun, Hepatobiliary and Pancreatic Interventional Treatment Center, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, China.
Email: 1307005@zju.edu.cn

hematopoietic stem cell transplantation or pyrrolizidine alkaloid ingestion, but more evidence is required to make an accurate diagnosis. Importantly, we speculate that HVOD is a rare characteristic of liver involvement in systemic amyloidosis.

Keywords
Systemic amyloidosis, hepatic veno-occlusive disease (HVOD), hepatomegaly, computed tomography, liver, purpura

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Introduction

Hepatic veno-occlusive disease (HVOD) is defined as obstruction of the sublobular veins or the central veins of the hepatic lobules, which results in intrahepatic or postsinusoidal portal hypertension.[1] The clinical manifestations of HVOD include upper right abdominal pain, hepatomegaly, ascites, weight gain, jaundice, and other digestive dysfunctions.[1] HVOD may be induced by ingestion of pyrrolizidine alkaloids (PAs), graft-versus-host disease after hematopoietic stem cell transplantation (HSCT), oral contraceptives, and radiation injury.[1–3]

Amyloidosis is a rare disease characterized by deposition of insoluble, fibril-forming amyloid proteins in the extracellular space of organs, and it can result in end-organ dysfunction. Systemic light-chain amyloidosis is the most common form of amyloidosis and results from plasma cell dyscrasia, which produces abnormal amounts of immunoglobulin light chains that can deposit in organs, such as the liver, heart, kidney, and peripheral nerves.[4,5] Patients with hepatic amyloidosis often present with hepatomegaly,[6] which is common in the patients HVOD.[7] We report a rare case of suspected HVOD, which was later diagnosed as systemic light-chain amyloidosis. The relevant literature is also reviewed for a systematic reference.

Case report

In June 2016, a 63-year-old man presented to our hospital with a 6-month history of upper abdominal pain, ascites, and weight loss of approximately 10 kg. Computed tomography (CT) of his abdomen showed that all branches of the hepatic vein were invisible and there was no space-occupying lesion in the enlarged liver (Figure 1a, b). The patient had an uncertain history of external application of a Chinese herbal medicine for trauma in the right hypochondriac region 1 month before this hospital visit. HVOD was initially suspected. Laboratory data showed high total cholesterol, low-density lipoprotein, and very low-density lipoprotein levels. Liver function, a routine blood test, coagulation function, and rheumatoid factors were in the normal range. The patient was suggested to undergo a transjugular intrahepatic portosystemic shunt. However, he refused this procedure and only intended to accept supportive treatment. Three months later, multiple purpura occurred in the skin (Figure 2).

In February 2017, the patient was admitted to our hospital with the complaint of pitting edema, and numbness and pain appeared in the lower legs and feet 1 month before this admission. Laboratory data were as follows (with normal values): serum albumin level, 24.3 g/L (35.0–55.0 g/L); globulin level, 18.9 g/L (20.0–35.0 g/L); aspartate aminotransferase level, 37 U/L (0–40 U/L);

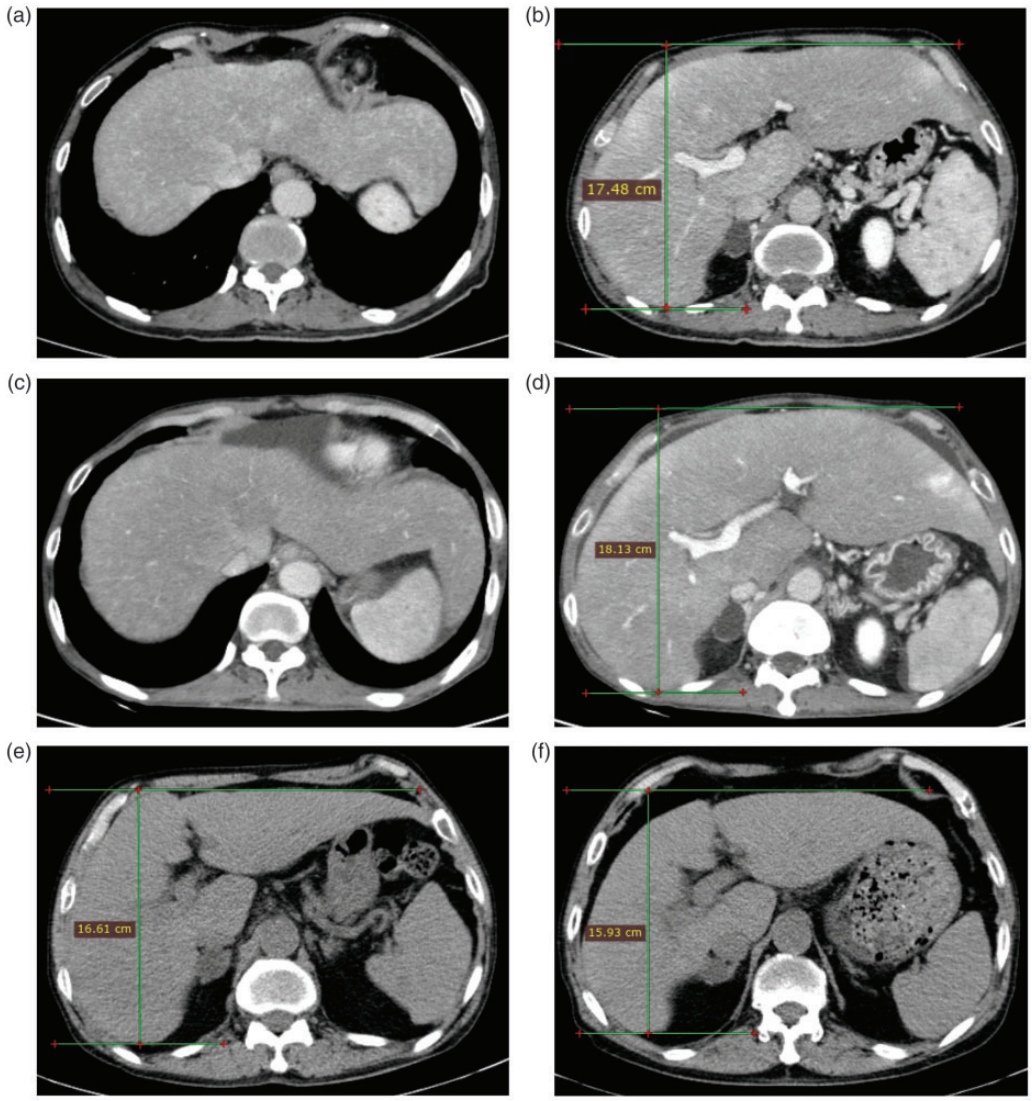

Figure 1. A computed tomography scan shows that, before appropriate treatment, all branches of the hepatic vein are invisible (a, c) and the liver became increasingly larger (b, d) in June 2016 (a, b) and February 2017 (c, d). A computed tomography follow-up at 13 (e) and 19 (f) months after treatment for systemic light-chain amyloidosis shows that the size of the liver has decreased, similar to a normal liver.

alanine aminotransferase level, 24 U/L (0–40 U/L); total bilirubin level, 0.47 mg/dL (0.2–1 mg/dL); glutamyl transpeptidase level, 746 U/L (11–50 U/L); alkaline phosphatase level, 167 U/L (40–150 U/L); total cholesterol level, 8.62 mmol/L (3.14–5.86 mmol/L); low density lipoprotein level, 5.57 mmol/L (1.31–3.29 mmol/L); and very low density lipoprotein level, 2.16 mmol/L (0.31–1.25 mmol/L). A routine blood test, international normalized radio, activated partial thromboplastin time, prothrombin time, and tumor markers were in the normal range, and serology results for hepatitis B

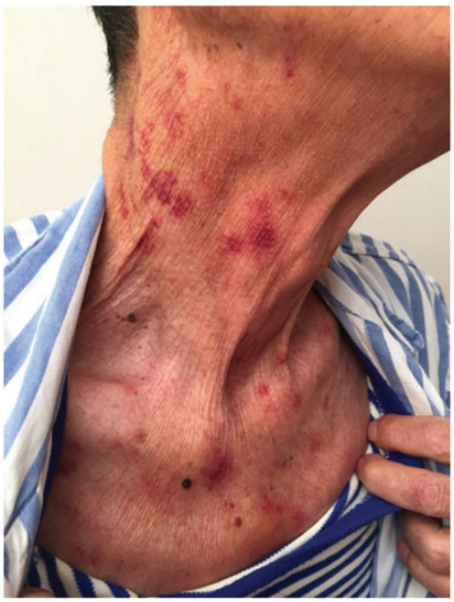

Figure 2. Photograph showing multiple purpura in the skin of the neck after a gentle scratching.

and C viruses were negative. CT arteriography of the liver showed hepatomegaly, splenomegaly, mild ascites, and invisible hepatic veins in the portal venous and equilibrium phase (Figure 1c, d). Therefore, HVOD was suspected. Because the patient had multiple patchy purpura and normal coagulation function, a hematological consultant suggested investigation of amyloidosis.

An ultrasound examination of the heart showed symmetrical thickening of the left ventricular wall with an interventricular septum of 1.7 cm and left ventricular posterior wall of 1.6 cm, diffuse thickening of the right ventricular wall of 0.62 cm, and a left ventricular ejection fraction of 56%. An electrocardiogram was performed and it showed incomplete right bundle branch block and left anterior fascicular block.

Urinalysis showed 3.41 g (0–0.2 g) of proteinuria every 24 hours and the serum $\beta 2$ microglobulin level was 5.65 mg/L (1.09–2.52 mg/L). Renal function showed a glomerular filtration rate of 85.51 mL/minute, serum urea level of 7.0 mmol/L (2.9–8.20 mmol/L), serum creatinine level of 82 μmol/L (59–104 μmol/L), and serum uric acid level of 483 μmol/L. Serum immunoelectrophoresis showed monoclonal κ light-chain and immunoglobulin G spikes. In urine, the immunoglobulin κ light-chain level was 40.20 mg/dL (0–1.85 mg/dL) and the immunoglobulin λ light-chain level was less than 5 mg/dL (0–5 mg/dL). In serum, the immunoglobulin κ light-chain level was 473.0 mg/dL (574–1280 mg/dL) and the immunoglobulin λ light-chain level was 172.0 mg/dL (269–638 mg/dL). A bone marrow core biopsy showed amyloid deposition by Congo red dye (Figure 3). Bone marrow aspirate showed 9% plasma cells. These examinations confirmed the diagnosis of systemic light-chain amyloidosis. The patient was then diagnosed with systemic light-chain amyloidosis involving the liver, heart, kidney, skin, and nerves.

In the following 3 months, the patient received treatment of bortezomib (1.6 mg/day on days 1, 8, 15, and 22) and dexamethasone (20 mg/day on days 1–2, 8–9, 15–16, and 22–23), and encouraging results were obtained. The N-terminal pro-brain natriuretic peptide level was decreased to 643 pg/mL (0–80 pg/mL) from 1174 pg/mL and serum immunoelectrophoresis showed that all types of immunoglobulins were negative. Ultrasound examination of the heart showed that the thickness of the interventricular septum was decreased to 1.3 cm (vs 1.7 cm in February 2017). Additionally, the left ventricular posterior wall thickness was decreased to 1.3 cm and the left ventricular ejection fraction was increased to 63%. After further continuous treatment for 4 months, ultrasound of the heart showed that the thicknesses of the interventricular septum, left ventricular posterior wall, and right ventricular wall were in the normal range, and the left ventricular ejection fraction was 66.7%. A CT scan showed that the

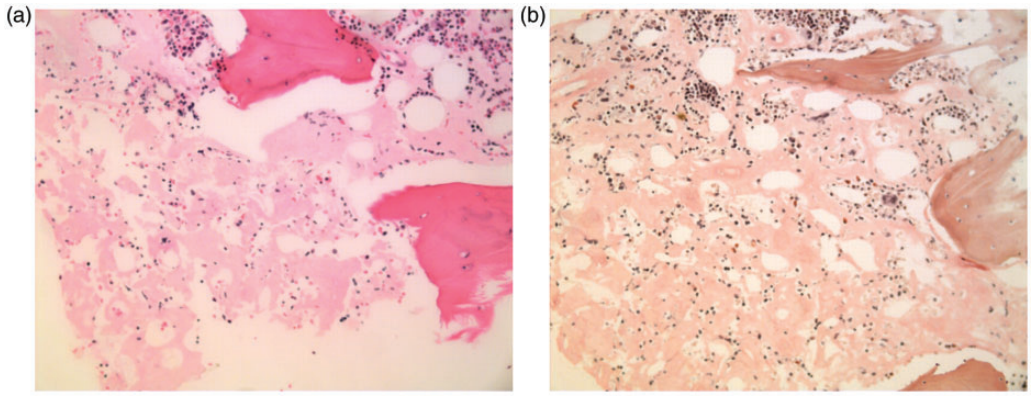

Figure 3. Bone biopsy showing extensive extracellular deposition of amorphous eosinophilic material (a, hematoxylin and eosin, ×200), which appears red with the Congo red stain (b, ×200).

superoinferior diameter of the liver was decreased to 17.5 cm (vs 20.2 cm in February 2017). A liver function test showed that the alkaline phosphatase level was decreased to 99 U/L, and albumin, total bilirubin, aspartate aminotransferase, and alanine aminotransferase levels were in the normal range. At the last follow-up in 28 March 2019, when the patient had received 10 chemotherapy cycles, the diameters of the liver and heart were in the normal range, and liver and kidney function tests were also in the normal range. Accordingly, the patient's symptoms of abdominal pain, ascites, and numbness and pain in his legs were greatly relieved.

This study was approved by the ethics committee of The First Affiliated Hospital, College of Medicine, Zhejiang University. The patient provided consent to publish medical information on his disease.

Discussion

Systemic light-chain amyloidosis is an infiltrative disorder that is associated with underlying plasma cell dyscrasia, in which monoclonal immunoglobulin light chains accumulate in an abnormal misfolded form as amyloid fibrils in the extracellular space.[8] Multiple organs, such as the heart, kidney, liver, and peripheral nervous system, can be involved in systemic light-chain amyloidosis, and ultimately, organ dysfunction occurs. Liver involvement of amyloidosis usually presents with a nonspecific clinical diagnosis, such as weight loss and fatigue, and hepatomegaly in imaging findings. The most important CT and magnetic resonance imaging findings of hepatic involvement in systemic amyloidosis are hepatomegaly, a heterogeneous appearance of the liver, and periportal involvement.[9,10] Kim et al.[11] found that asymmetric hepatomegaly of an atriangular shape with an apex at the falciform ligament and heterogeneous attenuation may help to differentiate amyloidosis from other infiltrative diseases. However, hepatomegaly and ascites can also be the most common CT findings of HVOD, but they are unspecific. Other CT features include heterogeneous hypoattenuation and patchy liver enhancement, with or without an invisible or narrow hepatic veins in the portal venous or equilibrium phase. However, a detailed history of using herbal medicine containing PAs or receiving HSCT is required to confirm the diagnosis of HVOD.[7,12] In our case, CT imaging showed giant hepatomegaly, mild ascites, invisible

hepatic veins, and homogeneous enhancement, which were different from radiological findings in HVOD or hepatic amyloidosis. Because of the radiological findings and uncertain history of using Chinese herbal medicine, the patient was initially diagnosed with HVOD. The treatment of HVOD is mainly based on anticoagulation and antithrombotic agents in addition to supportive and liver protective treatments. A transjugular intrahepatic portosystemic shunt is used for treating portal hypertension-related complications and clinical symptoms.[12] However, our patient declined a transjugular intrahepatic portosystemic shunt and received supportive therapy instead. In review of this case, we consider that fatigue, weight loss, and hepatomegaly with normal imaging may be signs of amyloidosis;[13,14] however, these signs are nonspecific and a diagnostic protocol should be started immediately.

In our patient, more symptoms of amyloidosis, such as purpura, peripheral edema, and peripheral neuropathy, appeared several months later. Therefore, we performed a series of investigations to confirm the diagnosis and assess amyloid-related organ damage. Demonstration of amyloid deposition in a tissue biopsy by Congo red staining remains the gold standard.[8,13] Because of a negative outcome of abdominal fat biopsy in our patient, a bone marrow biopsy was performed to show amyloid deposition by Congo red dye. A liver biopsy could have been performed to further determine the etiology of the patient's hepatomegaly for distinguishing amyloidosis from HVOD. However, because of the hemorrhagic tendency, with oozing at puncture points of the abdominal fat biopsy and bone marrow biopsy, as well as marked hepatic congestion, percutaneous liver biopsy was not performed to avoid bleeding that may lead to fatal consequences. Although the patient was eligible for transjugular biopsy, we could not collect liver tissue for making a pathological diagnosis because of a lack of a special biopsy laboratory. After treatment for amyloidosis, the hepatomegaly recovered to a normal size, liver function was in the normal range, and the patient's abdominal pain was greatly relieved. Therefore, we clinically diagnosed the patient with liver involvement in systemic amyloidosis. Unfortunately, the patient has not had a follow-up enhanced CT scan to evaluate venous patency.

Treatment of systemic light-chain amyloidosis includes combinations of bortezomib (cyclophosphamide, bortezomib, and dexamethasone), melphalan (melphalan and dexamethasone), thalidomide (cyclophosphamide, thalidomide, and dexamethasone), and lenalidomide (lenalidomide and dexamethasone). High-dose melphalan in combination with autologous stem cell transplantation is associated with excellent clinical outcomes.[8,13–15] Liver transplantation is a treatment option for systemic light-chain amyloidosis with dominant hepatic involvement.[16] There is excessive risk of treatment-related mortality in certain individuals with light-chain amyloidosis, particularly in those with substantial cardiac or autonomic nerve involvement. Therefore, our patient received a treatment cycle of bortezomib and dexamethasone to reduce the risk of serious complications. Fortunately, the patient tolerated the treatment well and benefited from the treatment.

Hepatic vein occlusion may be a rare presentation in systemic light-chain amyloidosis with liver involvement. The diagnosis of HVOD is controversial in patients without a definite history of HSCT or PAs. Searching for more evidence to confirm the diagnosis is important to ensure that the patient receives appropriate treatment and achieves a good prognosis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iDs

Tong-Yin Zhu https://orcid.org/0000-0002-8135-3793
Guan-Hui Zhou https://orcid.org/0000-0001-7856-0815

References

1. DeLeve L, Valla D and Garcia-Tsao G. Vascular disorders of the liver. *Hepatology* 2009; 49: 1729–1764.
2. Chojkier M. Hepatic sinusoidal-obstruction syndrome: toxicity of pyrrolizidine alkaloids. *J Hepatol* 2003; 39: 437–446.
3. Dai N, Yu Y, Ren T, et al. Gynura root induces hepatic veno-occlusive disease: a case report and review of the literature. *World J Gastroenterol* 2007; 13: 1628–1631.
4. Fernández de Larrea C, Verga L, Morbini P, et al. A practical approach to the diagnosis of systemic amyloidoses. *Blood* 2015; 125: 2239–2244.
5. Nuvolone M and Merlini G. Emerging therapeutic targets currently under investigation for the treatment of systemic amyloidosis. *Expert Opin Ther Targets* 2017; 21: 1095–1110.
6. Lovat L, Persey M, Madhoo S, et al. The liver in systemic amyloidosis: insights from 123I serum amyloid P component scintigraphy in 484 patients. *Gut* 1998; 42: 727–734.
7. Yang S, Wu J and Lei S. CT features of hepatic veno-occlusive disease: a meta-analysis. *Acad Radiol* 2018; 25: 328–337.
8. Zumbo G, Sadeghi-Alavijeh O, Hawkins PN, et al. New and developing therapies for AL amyloidosis. *Expert Opin Pharmacother* 2017; 18: 139–149.
9. Mainenti PP, D'Agostino L, Soscia E, et al. Hepatic and splenic amyloidosis: dual-phase spiral CT findings. *Abdom Imaging* 2003; 28: 688–690.
10. Ozcan HN, Haliloglu M, Sokmensuer C, et al. Imaging for abdominal involvement in amyloidosis. *Diagn Interv Radiol* 2017; 23: 282–285.
11. Kim SH, Han JK, Lee KH, et al. Abdominal amyloidosis: spectrum of radiological findings. *Clin Radiol* 2003; 58: 610–620.
12. Zhuge Y, Wang Y, Zhang F, et al. Clinical characteristics and treatment of pyrrolizidine alkaloid-related hepatic vein occlusive disease. *Liver Int* 2018; 38: 1867–1874.
13. Merlini G, Wechalekar AD and Palladini G. Systemic light chain amyloidosis: an update for treating physicians. *Blood* 2013; 121: 5124–5130.
14. Gillmore JD and Hawkins PN. Pathophysiology and treatment of systemic amyloidosis. *Nat Rev Nephrol* 2013; 9: 574–586.
15. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. *Blood* 2011; 118: 865–873.
16. Ueno A, Katoh N, Aramaki O, et al. Liver transplantation is a potential treatment option for systemic light chain amyloidosis patients with dominant hepatic involvement: a case report and analytical review of the literature. *Intern Med* 2016; 55: 1585–1590.