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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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CASE REPORT

Hepatomegaly and jaundice as the presenting symptoms of systemic light-chain amyloidosis: A case report

Xu Zhang, Fei Tang, Yan-Ying Gao, De-Zhao Song, Jing Liang

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Abstract

BACKGROUND

Light chain (AL) amyloidosis is a plasma cell dyscrasia characterized by the pathologic production and extracellular tissue deposition of fibrillar proteins derived from immunoglobulin AL fragments secreted by a clone of plasma cells, which leads to progressive dysfunction of the affected organs. The two most commonly affected organs are the heart and kidneys, and liver is rarely the dominant affected organ with only 3.9% of cases, making them prone to misdiagnosis and missed diagnosis.

CASE SUMMARY

A 65-year-old woman was admitted with a 3-mo history of progressive jaundice and marked hepatomegaly. Initially, based on enhanced computed tomography scan and angiography, Budd-Chiari syndrome was considered and balloon dilatation of significant hepatic vein stenoses was performed. However, additional diagnostic procedures, including liver biopsy and bone marrow-examination, revealed immunoglobulin kapa AL amyloidosis with extensive liver involvement and hepatic vascular compression. The disease course was progressive and fatal, and the patient eventually died 5 mo after initial presentation of symptoms.

CONCLUSION

AL amyloidosis with isolated liver involvement is very rare, and can be easily misdiagnosed as a vascular disease.

Key Words: Jaundice; Hepatomegaly; Liver amyloidosis; Kappa light chain; Pseudo-Budd-Chiari syndrome; Case report

Core Tip: Light chain (AL) amyloidosis is a systemic disease, with heart, kidneys, and peripheral nerves being the most commonly affected organs. The proportion of patients with only liver involvement alone is quite low, and these patients are highly prone to misdiagnosis and missed diagnosis. We present a case of AL amyloidosis with isolated liver involvement and severe cholestasis as the predominant manifestations.

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INTRODUCTION

Systemic light chain (AL) amyloidosis can affect all organs except the central nervous system[1]. The most frequently affected organs are the kidneys and the heart, either separately or combined[2]. Although hepatic deposition of AL amyloid is prevalent, it is usually clinically silent, and the liver is rarely the most severely affected organ[3]. 33%-92% of patients experience liver enlargement due to the accumulation of hepatic amyloid proteins and moderate-to-severe cholestasis[4]. Cases with jaundice as the primary manifestation are rare, accounting for less than 5% of documented cases [5]. AL amyloidosis, characterized by hepatomegaly and jaundice, is easily confused with diseases such as lymphoma, drug-induced liver injury (DILI), sinusoidal obstruction syndrome (SOS), and Budd-Chiari syndrome. Here, we report the case of a 64-year-old woman diagnosed with liver enlargement and progressive jaundice without obvious involvement of other organs. Diagnosis could not be ascertained by medical history, physical examination, or laboratory examination. Finally, the diagnosis of hepatic amyloidosis was confirmed by transjugular liver biopsy. Immunofluorescence, flow cytometry, and bone marrow smear further confirmed the diagnosis of AL amyloidosis.

CASE PRESENTATION

Chief complaints

A 64-year-old female patient was transferred to our hospital with progressive jaundice that had persisted for 3 mo.

History of present illness

The patient had developed jaundice without obvious causes over the previous 3 mo, accompanied by decreased appetite. For 4 wk, diammonium glycyrrhizinate and ursodeoxycholic acid were given in conjunction with Chinese herbal medicines. However, the jaundice gradually worsened.

History of past illness

The patient had undergone hysterectomy for uterine fibroids 18 years previously and cholecystectomy for cholecystitis 6 years ago. Preoperative examination revealed abnormal liver function manifested as elevated alkaline phosphatase (ALP) and glutamyl transpeptidase (GGT) levels. Liver tests were negative for hepatitis viruses, autoimmune liver disease, and metabolic liver disease. The cause of liver damage was not identified. After more than 2 mo of treatment with ursodeoxycholic acid, it was discontinued without further treatment or follow-up.

Personal and family history

The patient had no history of habitual alcohol consumption and no significant history of liver injury-inducing drug exposure. The patient had no chronic or familial inherited diseases.

Physical examination

Physical examination revealed marked jaundice, cutaneous spider naevi and an enlarged, hard, non-tender liver.

Laboratory examinations

The patient's liver function profile showed the following: Total bilirubin, 197.2 μmol/L (normal range: 3.4-20.5 μmol/L); direct bilirubin, 149.0 μmol/L (normal range: 0-3.4 μmol/L); aspartate aminotransferase, 88 IU/L (normal range: 15-40 IU/L); alanine aminotransferase, 11 IU/L (normal range: 9-50 IU/L); gamma-glutamyl transferase, 245 U/L (normal range: 10-60 U/L); ALP, 457 U/L (normal range: 45-125 U/L). The patient's white blood cell count was 11.47 × 10^9/L

[normal range: (3.5-9.5) × 10^9/L]; her neutrophils were 73.2%. In addition, there were no abnormalities in routine coagulation, renal function, electrocardiogram, myocardial enzymes, or type B natriuretic peptide levels. Liver tests were negative for hepatitis viruses, autoimmune liver diseases, and metabolic liver diseases such as hepatolenticular degeneration and hemochromatosis. Carbohydrate antigen 199 levels were slightly increased at 138.0 U/mL (normal range: < 60 U/mL), and alpha fetoprotein levels were normal. Monoclonal immunoglobulins were not detected in the serum or urine using immunofixation electrophoresis.

Imaging examinations

Echocardiography indicated reduced left ventricular diastolic function and mitral regurgitation, while electrocardiography showed no abnormalities. Gastroscopy revealed small esophageal varices. Abdominal enhanced computed tomography revealed an enlarged liver and spleen, irregular liver contour, uneven density of the liver parenchyma, and nodular enhancement in the arterial phase (Figure 1). Angiography suggested staged stenosis of the right and middle hepatic veins with local occlusion at the entrance to the inferior vena cava. The inferior vena cava was slightly narrow, which may have been related to liver enlargement and compression. Budd-Chiari syndrome with occlusion of the hepatic vein was considered, and balloon dilatation was performed to dilate the narrow segment of the hepatic vein and resume the blood stream. Radionuclide bone imaging did not reveal any abnormalities.

Pathological examination

Liver biopsy was performed, and the hepatic venous pressure gradient (wedged hepatic venous pressure minus free hepatic venous pressure) was found to be 25 mmHg. Liver pathology suggested disruption of the structure of the hepatic lobules, hepatocellular atrophy, and deposition of pink amorphous material in the portal area, vascular wall, and sinusoids between the liver plates. Congo red staining was positive, indicating hepatic amyloidosis (Figure 2A-D). Bone marrow aspiration smear showed abnormal proliferation of plasma cell system (Figure 2E and F). Flow cytometry immunofluorescence revealed that 3.88% of monoclonal plasma cells were visible, with CD38+ and CD138+ immunophenotypes and intracellular immunoglobulin kappa AL restriction expression, supporting AL amyloidosis.

FINAL DIAGNOSIS

The final diagnosis of the presented case was liver involvement of AL amyloidosis.

TREATMENT

After the dilatation of the hepatic vein, the patient's liver function did not improve, but instead the jaundice deepened progressively. In addition to liver-protective drug therapy, a double-plasma molecular adsorption liver support system was added.

OUTCOME AND FOLLOW-UP

However, the patient's bilirubin levels gradually increased, reaching up to 540 μmol/L. The patient developed bloody ascites and was considered to have experienced spontaneous rupture and bleeding of the liver capsule. After antibiotic and diuretic treatment ascites resolved completely. Considering the risks and costs of related treatment drugs, such as daretozumab and bortezomib, the family decided not to follow the corresponding treatment. The further course of the disease was progressive and the patient eventually died 5 mo after the onset of jaundice.

DISCUSSION

AL amyloidosis is the most common form of systemic amyloidosis, accounting for 70% of all cases[6-8]. It is characterized by deposition of misfolded monoclonal ALs secreted from malignant plasma cell clones. The misfolded proteins form highly ordered beta pleated sheet configuration, with the contiguous beta pleated sheets winding together into an insoluble fibrillar configuration instead of the typical alpha helical pattern of most proteins[9], which deposit in tissues interfering with the normal function of organs[10]. The clinical manifestations depend on the organ preference for ALs and the degree of organ dysfunction. The most commonly affected organs include the kidneys, heart, liver, peripheral nervous system, soft tissue, gastrointestinal tract, and less commonly, the lungs[11]. The findings of a study examining the correlation between immunoglobulin free ALs and clinical characteristics in a cohort of 730 recently diagnosed individuals with AL amyloidosis indicate that the type of AL has an impact on the range of organ involvement; κ-AL has more involvement in gastrointestinal and liver, while renal involvement is more common in λ-AL patients[12]. λ-AL is more common than κ-AL; as reported the ratio of λ/κ is about 3.5[13], and the overall survival of the two is similar. The overall survival of patients is primarily influenced by the numerical disparity between the clonal light-chain and the other light-chain, patients exhibiting a higher numerical difference experience significantly diminished survival duration[12].

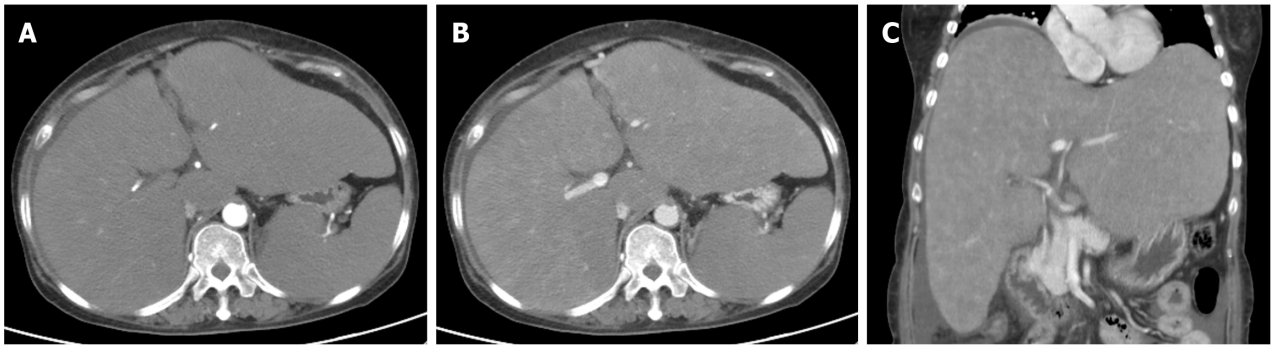

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Figure 1 Abdominal enhanced computed tomography images. A: Arterial phase; B: Portal vein phase; C: Coronal plane. The liver is significantly enlarged. The contour is irregular, the density of the parenchyma is reduced and uneven, and multiple nodular and punctate enhancements can be seen during the arterial phase. The spleen is enlarged.

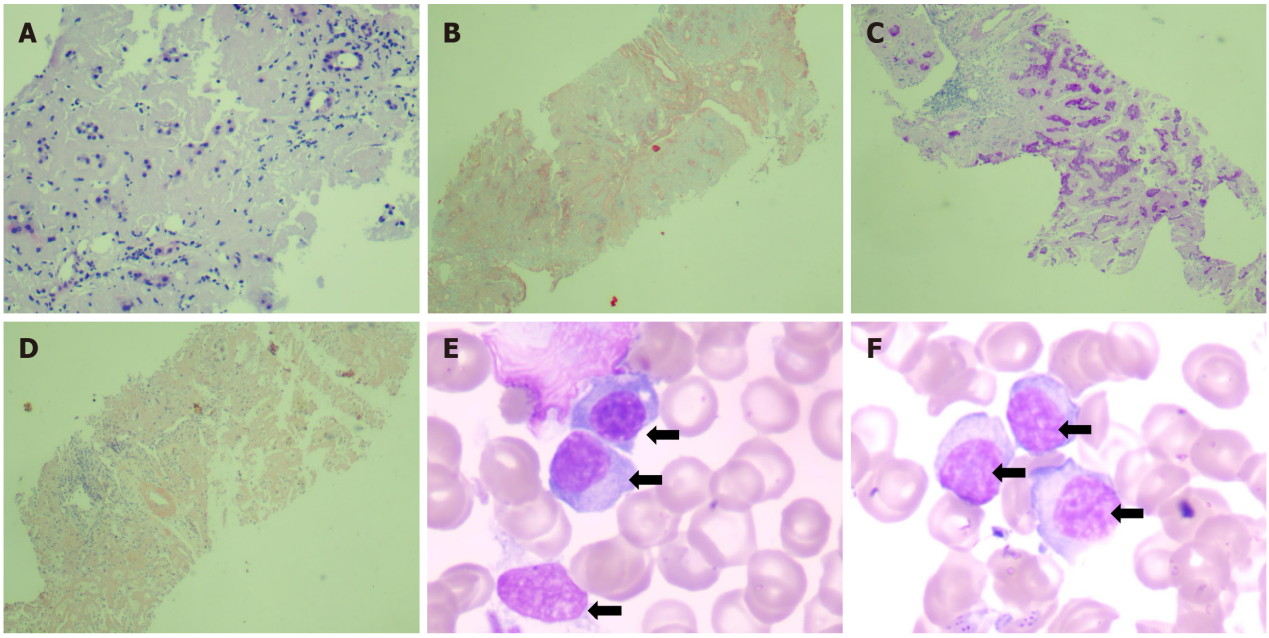

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Figure 2 Liver pathology and bone marrow aspiration smear. A: Hematoxylin-eosin staining (100 ×) showed deposition of pink fine-grained amorphous material in hepatic lobule and portal area, compression and deformation of liver plates, and atrophy of hepatocytes; B: Masson staining (40 ×) showed mild peri-sinusoidal fibrosis; C: Periodic acid-Schiff staining (40 ×) showed significant atrophy of liver cells with a few residual liver cells; D: Congo red staining (40 ×) indicated brick-red material deposition between liver cells; E and F: Bone marrow aspiration smear (100 ×) showed abnormal proliferation of plasma cell system. The cells are moderate-sized, the nucleus is large and eccentric, round or oval, the nuclear chromatin is fine, the cytoplasm is rich, blue, and foamy (black arrows).

The main manifestations in this patient were liver involvement, such as hepatomegaly and cholestasis, and no dysfunction of other organs such as the heart and kidneys. Flow cytometry immunofluorescence revealed monoclonal kappa chain restriction expression, which is consistent with previous reports[12].

Owing to the lack of specific symptoms, the time from the onset to diagnosis of AL amyloidosis is usually longer (6–10 mo) as reported previously[14-16]. A previous study showed that only 7.6% of patients were diagnosed with amyloidosis after consulting only one physician, whereas 31.8% of patients had consulted more than five physicians before being correctly diagnosed[1]. However, early diagnosis is crucial because early intervention can prevent irreversible organ damage and improve the prognosis. This patient had been diagnosed with abnormal liver function 6 years previously, mainly manifested by elevated ALP and GGT levels. Though liver disease-related investigations were performed; no clear cause was identified. Furthermore, the patient refrained from seeking subsequent medical intervention, resulting in a delayed diagnosis of the disease. Finally, when severe cholestasis occurred, the patient sought medical attention again, and a clear diagnosis was made based on liver pathology. Unfortunately, treatment opportunities were missed. The main symptoms of this case were progressive jaundice and liver enlargement. Therefore, we suggest that patients with unexplained elevated ALP and GGT levels accompanied by a significant increase in liver volume should be aware of the possibility of invasive diseases, such as liver amyloidosis.

Liver biopsy is not recommended as the first choice of evaluation for patients with suspected liver amyloidosis. Coagulation dysfunction is a recognized manifestation of AL amyloidosis. Multiple mechanisms have been proposed to explain this phenomenon, including vascular fragility caused by amyloid infiltration, presence of thrombin inhibitors, abnormal fibrinogen, potential disseminated intravascular coagulation and fibrinolysis, and acquired coagulation factor deficiency[17]. At the same time, due to excessive deposition of amyloid proteins, the liver enlarges and the tension of the liver capsule increases, posing a risk of spontaneous liver rupture. Therefore, percutaneous liver biopsy is associated with a high risk of inducing liver capsule rupture and abdominal bleeding. Subcutaneous fat biopsy or bone marrow biopsy can be considered when a liver biopsy is difficult to complete. The risks of both these tests is very low, with a comprehensive diagnostic sensitivity of 85%[18]. There are also reports suggesting that hepatocyte growth factor can serve as a useful non-invasive auxiliary marker for diagnosing primary systemic amyloidosis and predicting prognosis[19]. However, for patients with AL amyloidosis with only liver involvement, we can rely only on liver pathology to establish the diagnosis. Considering the risks of percutaneous liver biopsy, transjugular liver biopsy is a safe alternative method [20]. The patient was diagnosed based on the pathology obtained through a transjugular liver biopsy.

Hepatic AL amyloidosis is caused by excessive deposition of monoclonal globulin ALs or fragments produced by ALs in the liver tissue, mainly in the liver parenchyma, along the space of Disse, or in the vascular wall. When a large amount of amyloid protein is deposited in the liver, the liver cells are severely compressed and are likely to atrophy or disappear [21,22]. The pathological manifestations in this patient were consistent with the significant deposition of amyloid proteins, atrophy of liver cells, and destruction of lobular structures. Patients often exhibit liver enlargement and elevated cholestasis enzymes. Total bilirubin levels may also increase in some patients with advanced systemic hepatic amyloidosis. Because of the main manifestations of liver enlargement, jaundice, and even ascites, imaging findings indicating an uneven density of the liver parenchyma, as well as narrowing of the hepatic veins due to compression; these are similar to the manifestations of liver vascular diseases, such as acute Budd-Chiari syndrome and SOS, and are prone to be misdiagnosed. Our patient had a history of use of traditional Chinese herbal medicines, and we initially considered a diagnosis of SOS. However, after a detailed inquiry into the history of the present illness, it was found that the patient took non-standard drugs after the onset of jaundice, which did not meet the causal temporal relationship of the DILI diagnosis. Thus, the diagnosis of SOS remained unclear. In addition, during the transjugular liver biopsy, the patient underwent hepatic venography, which revealed stenosis of the right and middle hepatic veins. The interventional radiologists considered it to be consistent with the manifestation of Budd–Chiari syndrome and performed balloon dilation. However, in the end, the examination of liver pathology provided a definitive response, corroborating the notion that liver amyloidosis imitated Budd-Chiari syndrome rather than Budd-Chiari syndrome itself. We believe that the hepatic vein stenosis in this case was related to vascular compression caused by excessive deposition of amyloid in the liver. It is noteworthy that hepatic vascular diseases, such as Budd Chiari syndrome or SOS, commonly present with ascites in the early stages of the disease. However, in the early stages of hepatic amyloidosis, ascites rarely manifests, which could serve as a significant diagnostic differentiator.

Bortezomib is widely used for the treatment of AL amyloidosis. A chemotherapy regimen based on bortezomib can be used as a first-line treatment for newly diagnosed and relapsed patients[23]. However, patients with end-stage heart disease and liver failure are usually unsuitable for chemoimmunotherapy and cannot tolerate anti-clonal therapy that suppresses abnormal plasma cell clones[24,25]. Liver transplantation (LT) may be a practical alternative for patients with major liver involvement. In the literature on solid organ transplantation in AL amyloidosis, nine patients received orthotopic LT, and the 1-year and 5-year survival rates were 33% and 22%, respectively[26]. Among them, six patients received post-transplant chemotherapy, and interestingly, four patients with basal renal amyloidosis developed rapidly progressive proteinuria. Overall, the LT data of patients with AL amyloidosis are limited, and further exploration is needed. The patient lost effective treatment opportunities owing to severe liver damage and ultimately died of liver failure.

CONCLUSION

The liver, is often affected by AL amyloidosis in conjunction multiple organ involvement such as the heart and kidneys. Isolated liver involvement is rare. The number of organs affected by AL amyloidosis mainly depends on the light-chain phenotype. Hepatic amyloidosis is characterized by a mild elevation of cholestasis enzymes in the early stages without obvious clinical symptoms and signs, making timely diagnosis difficult. As the disease progresses, symptoms of liver enlargement and jaundice may occur, and it can be easily misdiagnosed as a vascular disease, such as SOS or Budd-Chiari syndrome. Severe cholestasis is associated with severe damage to the liver structure and function, indicating poor prognosis, poor tolerance to effective treatment drugs, and loss of effective treatment opportunities. Therefore, in populations with unexplained elevated ALP and GGT levels, we need to be vigilant about the possibility of liver amyloidosis.

FOOTNOTES

Co-first authors: Xu Zhang and Fei Tang.

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