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## **A case of ABCB4 gene mutation-associated cirrhosis with systemic amyloidosis**

ABCB4 gene mutation-associated cirrhosis with systemic amyloidosis

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### **Abstract**

#### **BACKGROUND**

ABCB4 mutation associated cirrhosis with systemic amyloidosis is rare.

#### **CASE SUMMARY**

The patient underwent liver, spleen, kidney, and bone marrow pathological biopsy, liver amyloidosis property profiling, genome-wide exon sequencing and other related examinations. The patient was ultimately diagnosed with ABCB4 mutation-related cirrhosis with amyloidosis.

#### **CONCLUSION**

This disease is rare in clinical practice and is easily misdiagnosed or missed. A literature review found that this type of report is rare, so the diagnosis and treatment of this patient were reported and analyzed.

**Key Words:** ABCB4 gene; cirrhosis; systemic amyloidosis; case report

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**Core Tip:** We report a case of ABCB4 mutation-associated cirrhosis with systemic amyloidosis. The patient underwent liver, spleen, kidney, and bone marrow pathological biopsy, liver amyloidosis property profiling, genome-wide exon sequencing and other related examinations. The patient was ultimately diagnosed with ABCB4 mutation-related cirrhosis with amyloidosis. This disease is rare in clinical practice and is easily misdiagnosed or missed. A literature review found that this type of report is rare, so the diagnosis and treatment of this patient were reported and analyzed.

## **INTRODUCTION**

Multi-drug resistance protein (MDR3) encoded by ABCB4 gene can transport phospholipids to bile, which plays an important role in normal bile formation. A mutation in the ABCB4 gene can result in bile duct damage and cholestasis. It is a chromosomal recessive genetic disorder with clinical indications of gallbladder/intrahepatic bile duct stones and recurrent jaundice. This condition is known as progressive familial intrahepatic cholestasis -3 (PFIC-3). Few patients can progress to portal hypertension, liver cirrhosis or even liver failure. Laboratory examination is characterized by persistent or repeated ALP ALP, GGT increase [1-2], and ursodeoxycholic acid is the main treatment drug [3].

The disease known as primary light chain amyloidosis is a condition that is both infrequent and untreatable. According to research, the occurrence of this ailment in Europe and America is estimated to be approximately 9-14 individuals per one million people per year [4]. The formation of amyloid protein is attributed to the misfolding of monoclonal immunoglobulin light chain. This protein is deposited in various tissues and organs, leading to the deterioration of tissue structure, organ dysfunction, and gradual advancement. The etiology of the condition is associated with the cytotoxicity of unbound light chain amyloid protein and the gradual deterioration of organ function due to tissue structure degradation [5]. The condition may affect various tissues or organs, including but not limited to the liver, kidney, nerve, heart, and gastrointestinal

tract, either successively or concurrently<sup>[6-7]</sup>. Because of the atypical and intricate symptoms of multiple organs and systems, early diagnosis and therapy are difficult, and the degree of pathological alterations in diverse tissues and organs in most individuals is irreversible when they are diagnosed.

In this study, a unique instance of liver cirrhosis resulting from a mutation in the ABCB4 gene in conjunction with primary light chain amyloidosis is presented. The disease exhibits clinical manifestations such as portal hypertension, recurrent ascites, and jaundice. Additionally, intractable proteinuria, peripheral neuropathy, and gradual cardiac function damage may also appear during the progression of the disease. Following an extensive four-year pursuit of medical intervention, a diagnosis was ultimately established, and the condition exhibited improvement subsequent to treatment with a combination of ursodeoxycholic acid and CD38 monoclonal antibody daratumumab.

## **CASE PRESENTATION**

### ***Chief complaints***

A 25-year-old woman found unexplained splenomegaly during her physical examination at the age of 18, and she felt no discomfort without further diagnosis and treatment.

### ***History of present illness***

The individual, who was 21 years old at the time, was admitted to the hospital in November 2018 due to recurring abdominal pain caused by calculous cholecystitis.

### ***History of past illness***

The patient recurring abdominal pain caused by calculous cholecystitis.

### ***Personal and family history***

No remarkable history.

### ***Physical examination***

The patient without tachycardia or fever (blood pressure, 122/80 mmHg; pulse rate, 72 bpm; body temperature, 36.6 °C). The patient mild tenderness in the upper right abdomen, soft abdomen, and palpable enlarged spleen in the left abdomen. She was not pale nor icteric.

### ***Laboratory examinations***

The results of the blood analysis indicated a noteworthy reduction in platelets (PLT33\*10<sup>9</sup>/L). This was attributed to hypersplenism resulting from splenomegaly. However, no additional investigation *via* bone marrow puncture was performed. Selective laparoscopic cholecystectomy and splenectomy were performed. Nodular changes were observed on the surface of the liver during the operation, and a small amount of liver tissue was procured for pathological analysis. The results of the laboratory tests for HBSAg, HCV-Ab, ceruloplasmin, iron, ferritin, ANA antibody spectrum, autoantibody against liver, anticardiolipin antibody, and antineutrophil were all negative. The etiology of liver cirrhosis remains unclear. Due to the apparent elevation of ALP and GGT in liver function, a dosage of ursodeoxycholic acid at a rate of 15 mg/kg/d was administered. During the month of July in the year 2020, an initial detection of positive urinary protein was made, which was followed by the onset of persistent proteinuria and hypoproteinemia. The patient received medical attention in the nephrology department with the purpose of excluding the possibility of rheumatism and immune-related ailments. However, the etiology of the condition remained undetermined.

The patient was hospitalized on January 26, 2022, due to experiencing abdominal pain, palpitation, and numbness in both lower limbs for a duration of two days. The results of the physical examination revealed tenderness in the upper abdominal region, along with the presence of ascites and edema in both lower extremities. No apparent jaundice of the skin and sclera was observed, and the nervous system exhibited normal

functioning. The results of the peripheral blood test indicated a significant increase in GGT and ALP levels, which are indicative of liver function impairment. However, renal function was found to be within normal limits. Additionally, the levels of N-brain natriuretic peptide precursor and troponin were significantly elevated, and an abnormality was observed in the electrocardiogram. The computed tomography scan of the upper abdomen revealed the presence of ascites, which is attributed to cirrhosis (Figure 2 ). The results of the urine routine analysis indicated a urinary protein level of 3+ and a 24-hour urinary protein level of 744.98mg/24 h. Following the administration of symptomatic treatment, there was an improvement in the symptoms exhibited by the patients. The etiology of liver cirrhosis, including but not limited to HBSAg, HCV-Ab, ceruloplasmin, ANA antibody spectrum, and autoantibodies, yielded negative findings. To investigate the etiology of liver cirrhosis, the exons of the entire genome of patients' peripheral blood were analyzed. The findings revealed the presence of a heterozygous mutation in the ABCB4 c.2318G> T gene (refer to Figure 3 for ECG, electromyography, and ABCB4 gene mutation sites). ABCB4 gene mutation is associated with several clinical manifestations, including cholecystolithiasis, bile duct injury, and cholestasis. In some cases, patients may progress to cirrhosis, as evidenced by persistent and significant abnormalities in GGT and ALP liver function tests. However, the development of additional symptoms, such as massive proteinuria, abnormal cardiac function indexes, and numbness in both lower limbs, suggests the presence of other factors contributing to the development of systemic multiple organ diseases. In light of the patient's splenomegaly of unknown etiology at the age of 18, is there a potential association with hematologic or neoplastic pathologies? Subsequent analysis revealed that the standard bone marrow examination indicated the presence of hyperplastic anemia, while the bone marrow biopsy indicated a significant decrease in the proliferation of hematopoietic tissue. The results of the serum and urine immunofixation electrophoresis tests were negative. The immune analysis of hematological tumors (specifically, bone marrow blood) did not yield any detection of monoclonal B cells. The results of the cardiac ultrasound and cardiac MRI+PYP

radionuclide scanning were found to be within normal limits. The PET-CT scan yielded negative results for tumor lesions. However, the levels of free  $\kappa$  and  $\lambda$  light chains in serum and urine increased (blood free  $\kappa$  light chain 45.41mg/L, blood free  $\lambda$  light chain 63.07mg/L, urine free  $\kappa$  light chain 72.40mg/L and urine free  $\lambda$  light chain 65.20mg/L). The results of the electromyography test indicated a decrease in the conduction velocity of the superficial peroneal nerve. The aforementioned findings suggest a potential presence of amyloidosis, however, a pathological assessment is required for confirmation. The liver and spleen pathological tissues that were preserved after the 2018 operation, as well as the bone marrow biopsy tissue from the current hospitalization, were subjected to Congo red staining with the permission of the patients and their families. The findings of the staining were uniformly positive. And further improve the renal puncture pathological tissue Congo red staining positive, immunohistochemical  $\kappa$  staining positive,  $\lambda$  staining negative. Liver mass spectrometry analysis also confirmed  $\kappa$  light chain amyloidosis (Figure 4 for histopathological examination of liver, spleen, kidney and bone marrow. Figure 5 for liver mass spectrometry analysis). Although heart involvement was suspected, the patient and his family refused the myocardial biopsy considering the danger, but the diagnosis basis of primary light chain ( $\kappa$ ) amyloidosis was very sufficient. At this point, the mystery of giant spleen with unknown etiology, persistent cirrhosis, proteinuria, peripheral neuropathy and cardiac function damage has finally been solved.

### *Imaging examinations*

A cholecystectomy was scheduled as a treatment plan. Prior to the surgical procedure, the computed tomography scan of the abdomen revealed the presence of an enlarged spleen, while the hepatic image morphology appeared to be within normal limits. The results of the gastroscopy indicated the presence of esophageal varices and portal hypertensive gastropathy.

The postoperative pathological diagnosis of the liver tissue revealed the presence of liver cirrhosis and bile duct injury. Supporting evidence for this diagnosis can be found

in Figure 1, which includes upper abdominal CT, gastroscopy, and pathological images of the liver and spleen. The individual refrained from consuming alcohol or using any form of drugs.

### **FINAL DIAGNOSIS**

ABCB4 gene mutation-associated cirrhosis with systemic amyloidosis

### **TREATMENT**

Following discharge, the patient adhered to the prescribed regimen of ursodeoxycholic acid and underwent regular monitoring. However, the progression of liver cirrhosis persisted, as evidenced by recurring ascites, melena, and jaundice. Following patient consultation, treatment with CD38 monoclonal antibody daratumumab (intravenous infusion, 900mg per administration, administered every other week) was initiated in March 2022.

### **OUTCOME AND FOLLOW-UP**

The urinary protein levels exhibited a negative result, while the free light chain present in both peripheral blood and urine returned to a standard level. Additionally, the electrocardiogram displayed a normal reading. The patient's bilateral lower limb numbness resolved and his clinical status remained stable. The individual in question is currently undergoing medical treatment and receiving frequent monitoring (Table 1).

### **DISCUSSION**

Progressive Familial Intrahepatic Cholestasis-3 (PFIC-3) is an autosomal recessive hereditary disease that arises from mutations in the ABCB4 gene. The incidence rate of this condition is notably low, with an average occurrence of 1 in 500,000 and predominantly sporadic in nature. The mutation of the ABCB4 gene results in the impairment of the MDR3 glycoprotein that is present in the membrane of the capillary



bile duct of hepatocytes. This leads to a disruption in the metabolism of bile acids, an elevation in the formation of cholesterol stones, damage to the bile duct, and the onset of intrahepatic cholestasis. The laboratory analysis indicates a continual elevation of serum GGT, along with hyperbilirubinemia primarily resulting from the increase in conjugated bilirubin. The histopathological examination of the liver reveals non-specific alterations, including intrahepatic bile duct damage and hyperplasia of fibrous tissue. The clinical manifestations of PFIC-3 frequently include gallbladder stones and chronic progressive liver damage. In some cases, affected patients may develop cirrhosis during late childhood or adolescence <sup>[1][8]</sup>. Currently, the administration of ursodeoxycholic acid is primarily oral in nature, with the aim of competing with primary bile acids for reabsorption in the small intestine. This approach is intended to mitigate the harm caused by cholestasis to liver cells. In cases of end-stage liver disease, liver transplantation is typically required. <sup>[9]</sup>.

AL amyloidosis is a disease that occurs infrequently in the population. European and American countries have reported an incidence rate of 8-10 cases per million person-years. The formation of amyloid protein is attributed to the misfolding of monoclonal immunoglobulin light chain, leading to its deposition in tissues and organs. This process results in the destruction of tissue structure, organ dysfunction, and the onset of progressive disease. The condition is primarily associated with the abnormal proliferation of clonal plasma cells, with a minor proportion being linked to lymphoproliferative diseases<sup>[10]</sup>. The amyloid protein exhibits the following characteristics: According to sources <sup>[11-12]</sup>, the staining of hematoxylin-eosin (HE) appears eosinophilic and homogeneous, while Congo red staining displays a brick red color. Additionally, the use of a polarization microscope results in apple green birefringence. In general, the biopsy positivity rate for symptomatic organs or tissues is greater than 95%, whereas for bone marrow, it ranges from 50% to 65%. Routine recommendation of myocardial biopsy is discouraged due to its high risk <sup>[13]</sup>. At present, the gold index of diagnosis is based on histopathological results and protein mass spectrometry analysis. According to the types of monoclonal light chain

deposition, it is divided into  $\lambda$  light chain type and  $\kappa$  light chain type. In clinic,  $\lambda$  light chain type is the main one, accounting for about 85%, and  $\kappa$  light chain type is rare. Due to the different involved tissues and organs, the clinical manifestations of the disease are diverse, which brings great difficulties to early diagnosis and treatment. Most patients often have irreversible functions of the involved tissues and organs when they are diagnosed. Autologous peripheral blood stem cell transplantation and targeted plasma cell therapy such as daratumumab are the main treatment schemes for amyloidosis at present.

The co-occurrence of PFIC-3 and systemic amyloidosis in a single patient has not been reported, likely due to the rarity of these diseases. The individual in question initially presented with unexplained splenomegaly and cholecystolithiasis. Subsequent diagnostic tests including liver function analysis, abdominal CT, gastroscopy, and liver histopathology confirmed the diagnosis of cirrhosis. However, the underlying etiology remains unclear. Subsequently, the state of liver cirrhosis has exhibited a progressive decline, with the involvement of numerous organs including the kidney, peripheral nerve, and heart. A heterozygous variation at the locus ABCB4 c.2318G>T was identified through gene sequencing. The liver tissue's pathological biopsy exhibited bile duct injury, cholestasis, and cirrhosis, which were in line with cirrhosis caused by PFIC-3, in conjunction with elevated GGT and ALP levels. Nonetheless, the ailment fails to account for the engagement of numerous bodily systems. Through further detection of Congo red staining in liver, spleen, kidney, bone marrow and other tissues of the patient, and mass spectrometry analysis of liver tissue amyloidosis, Ig $\kappa$  was highly expressed, and finally it was thoroughly and definitely diagnosed as rare PFIC-3 complicated with systemic light chain  $\kappa$  amyloidosis.

For the treatment of liver cirrhosis related to ABCB4 gene mutation, early use of ursodeoxycholic acid can improve cholestasis, delay the process of fibrosis, and thus improve the prognosis [3]. Anti-plasma cell therapy is the core treatment for systemic light chain  $\kappa$  amyloidosis, and daratumumab is a humanized IgG1- $\kappa$  monoclonal antibody targeting CD38 antigen on plasma cell surface. Studies have shown that this

drug can quickly achieve deep hematological remission and organ remission with good safety [14,15]. The patient's condition worsened after using ursodeoxycholic acid for a long period. We observed that after daratumumab treatment, the hematuria light chain dropped noticeably, the urine protein turned negative, and symptoms such as numbness and palpitation in both lower limbs disappeared. The treatment had a positive effect.

In conjunction with the aforementioned instance, we possess the subsequent encounter: ①The majority of experts tend to have a limited scope of expertise and may overlook the potential existence of alternative illnesses. ②Patients diagnosed with liver cirrhosis exhibiting elevated levels of ALP and GGT, coupled with unknown bile duct changes in liver biopsy, may benefit from undergoing genetic testing to identify rare genetic disorders such as liver lesions caused by ABCB4 gene mutation. ③The involvement of multiple organs, including the liver, kidney, heart, and peripheral nervous system, in systemic amyloidosis results in complex and inconspicuous clinical manifestations, posing challenges for early diagnosis and treatment. The determination of the diagnosis is reliant upon the utilization of Congo red staining for tissue biopsy and the analysis of protein mass spectrometry. ④Liver transplantation is the preferred treatment option for individuals with liver-limited amyloidosis.

## **CONCLUSION**

For systemic amyloidosis affecting multiple tissues and organs throughout the body, the current therapeutic approach involves the utilization of CD38 monoclonal antibody drug regimens. The administration of anti-plasma cell therapy in the early stages, along with symptomatic treatment, has been found to be beneficial in enhancing clinical symptoms and extending the duration of survival, as per previous research.

ORIGINALITY REPORT

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PRIMARY SOURCES

1

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