Ductopenia and cirrhosis in a 32-year-old woman with progressive familial intrahepatic cholestasis type 3: A case report and review of the literature

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Abstract

Progressive familial intrahepatic cholestasis type 3 is caused by a mutation in the ATP-binding cassette, subfamily B, member 4 (ABCB4) gene encoding multidrug resistance protein 3. A 32-year-old woman with a history of acute hepatitis at age 9 years was found to have jaundice during pregnancy in 2008, and was diagnosed as having intrahepatic cholestasis of pregnancy. In 2009, she underwent cholecystectomy for gallstones and chronic cholecystitis. However, itching and jaundice did not resolve postoperatively. She was admitted to our hospital with fatigue, jaundice, and a recently elevated γ-glutamyl transpeptidase level. Liver biopsy led to the diagnosis of biliary cirrhosis with ductopenia. Genetic testing revealed a pathogenic heterozygous mutation, ex13 c.1531G > A (p.A511T), in the ABCB4 gene. Her father did not carry the mutation, but her mother’s brother carried the heterozygous mutation. We made a definitive
diagnosis of familial intrahepatic cholestasis type 3. Her symptoms and liver function improved after 3 mo of treatment with ursodeoxycholic acid.

**Key words:** Cirrhosis; Progressive familial intrahepatic cholestasis type 3; Case report

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Core tip: A 32-year-old woman with a history of acute hepatitis at age 9 years was diagnosed as having intrahepatic cholestasis of pregnancy in 2008. In 2009, she underwent cholecystectomy for gallstones and chronic cholecystitis. However, itching and jaundice did not resolve postoperatively. She was admitted with fatigue, jaundice, and a recently elevated \( \gamma \)-glutamyl transpeptidase level. Liver biopsy led to the diagnosis of biliary cirrhosis with ductopenia. Genetic testing revealed a pathogenic heterozygous mutation, ex13 c.1531G > A (p.A511T), in the ATP-binding cassette, subfamily B, member 4 gene. We made a definitive diagnosis of familial intrahepatic cholestasis type 3.

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**INTRODUCTION**

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is caused by a mutation in the ATP-binding cassette, subfamily B, member 4 (ABCB4) gene encoding multidrug resistance protein 3 (MDR3) \([1,2]\), PFIC3 is characterized by recurrent itching, jaundice, white clay-like stool, hepatosplenomegaly, and gastrointestinal bleeding, often progressing to cirrhosis and liver failure before adulthood \([3,4]\). PFIC3 is a subtype of progressive familial intrahepatic cholestasis that differs from PFIC1 and PFIC2 in that serum \( \gamma \)-glutamyl transpeptidase (GGT) is elevated \([5]\). The pathological manifestations of liver tissue include obvious ductopenia or interlobular bile duct hyperplasia and terminal bile duct biliary sludge formation rather than abnormal synthesis of bile \([6,8]\). The incidence is 1/500000. However, reports of PFIC3 with high GGT are rare. We present the case of a patient with a mutant gene fragment in PFIC3, which has not been previously reported in the East Asian population.

The study was approved by the Medical Ethics Committee of the Third Hospital of Zhenjiang Affiliated Jiangsu University, and written informed consent was obtained from the patient. The study was conducted in accordance with the Declaration of Helsinki.

**CASE REPORT**

A 32-year-old woman with a history of acute hepatitis at age 9 years was admitted to a local hospital for an unknown disease process. She was discharged after 10 d of treatment and recovered from her condition. During pregnancy in 2008, she developed jaundice and was diagnosed as having intrahepatic cholestasis of pregnancy (ICP). In the 2 years after delivery, she experienced recurrent itching and jaundice. She underwent cholecystectomy for gallstones and chronic cholecystitis detected on ultrasound. However, her itching and jaundice did not resolve postoperatively, and high serum total bilirubin (TBIL) was repeatedly observed, with the highest level of > 100 \( \mu \)mol/L. Alkaline phosphatase (ALP) and GGT were also repeatedly increased and remained at 5-10 times the upper limit of normal.

She was admitted to our hospital with fatigue, jaundice, and decreased food intake during the prior week. Liver function tests showed the following results: TBIL 59.8 \( \mu \)mol/L, direct bilirubin 34.6 \( \mu \)mol/L, serum total protein 64.5 g/L, albumin 37.5 g/L, alanine aminotransferase (ALT) 123 U/L, aspartate aminotransferase (AST) 127 U/L, aspartate transaminase 117 U/L, ALP 371 U/L, and GGT 252 U/L. Coagulation tests showed prothrombin time of 16.3 s, an international normalized ratio of 1.43, and activated partial thromboplastin time of 44.1 s. Routine blood tests showed the following results: White blood cells 2.71 \( \times \) 10^9/L, red blood cells 3.77 \( \times \) 10^12/L, hemoglobin 120 g/L, platelets 67 \( \times \) 10^9/L, and neutrophils 64.3%. Antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody type 1, anti-nuclear glycoprotein antibody, anti-soluble acid nucleoprotein antibody, anti-hepatocyte cytoplasmic antigen type 1 antibody, anti-soluble liver antigen/hepatopancreatic antigen antibody, and other tests were negative, whereas the immunoglobulin G and immunoglobulin M levels were 11.4 g/L (< 17.1 g/L) and 1.2 g/L (< 4 g/L), respectively. Viral hepatitis (A-E), Epstein-Barr virus, and cytomegalovirus infections were ruled out. Computed tomography of the upper abdomen revealed cirrhosis, splenomegaly, ascites, and intrahepatic bile duct stones.

Liver biopsy led to the diagnosis of biliary cirrhosis with ductopenia (Figure 1). Genetic testing was performed for all 254 exons of liver disease-related genes, and adjacent ± 10 bp introns were sequenced. The results revealed a pathogenic heterozygous mutation, ex13 c.1531G > A (p.A511T), in the ABCB4 gene (Figure 2).

Her father did not carry the mutation, but her mother’s brother carried the heterozygous mutation and her mother died of cirrhosis at age 62 years. We made a definitive diagnosis of PFIC3. Her symptoms and liver function tests improved after 3 mo of treatment with ursodeoxycholic acid. The results of serum tests after treatment were as follows: Albumin 37.1 g/L, TBIL 21.9 \( \mu \)mol/L, ALT 58 U/L, ALP 127 U/L, and GGT 127 U/L.
DISCUSSION
PFIC is a group of autosomal recessive genetic diseases that cause bile excretion disorders due to mutations. The clinical manifestations of intrahepatic cholestasis usually present in infancy or childhood, eventually leading to liver failure. PFIC is mainly divided into three types: PFIC1, which is caused by an ATP8B1 gene mutation, resulting in a P-type ATPase-FICl defect encoded by the gene; PFIC2, which is derived from a mutation in the ABCBI1 gene encoding for bile salt export pump protein; and PFIC3, which is caused by a mutation in the ABCB4 gene encoding MDR3.

PFIC3 is a subtype of progressive familial intrahepatic cholestasis, and its main difference from PFIC1 and PFIC2 is the presence of elevated GGT\(^{[9,10]}\). PFIC3 is characterized by recurrent itching, jaundice, white clay-like stools, hepatosplenomegaly, and gastrointestinal bleeding, often progressing to cirrhosis and liver failure before adulthood\(^{[11]}\).

PFIC3 is a rare disease, mostly sporadic, and the incidence rate has not been accurately reported. According to a survey, the estimated incidence is 1/500000 (http://demo.istat.it/).

The MDR3 protein encoded by the ABCB4 gene is located on the hepatic capillary bile duct membrane. It is a phospholipid export pump and phospholipid flipping enzyme, and transports phospholipids from liver cells into the bile duct, which is the rate-limiting step of phospholipid secretion. Under normal circumstances, phospholipids synthesized by hepatocytes are transported into bile by MDR3. Together with bile salts, the phospholipids form microparticles, which increase the hydrophilicity and reduce the descaling effect of bile salts, and protect bile duct cells from toxic damage caused by bile salts. Mutation in the ABCB4 gene results in the loss of expression of the MDR3 protein associated with phospholipid secretion in the bile duct. With the lack of phospholipids in bile, the formation of mixed particles of bile salts and phospholipids is reduced, resulting in the release of bile salts and causing toxic and detergent effects on the capillary bile duct membrane. When the biliary cells are damaged, cholestasis, small bile duct hyperplasia, inflammatory infiltration, and gradual progression to portal fibrosis, cirrhosis, and portal hypertension occur. Patients often die from liver failure.

More than 40 different ABCB4 gene mutations have been reported\(^{[12]}\), including missense mutations, nonsense mutations, deletion mutations, and insertion of small fragment bases. The severity of the disease is related to the type of gene mutation. Nonsense mutations and deletion mutations are more likely to have serious clinical symptoms. When family members are homozygous for a mutation, they present with progressive intrahepatic cholestasis, often requiring liver transplantation in early childhood or leading to death due to liver failure\(^{[13,14]}\).

When family members are heterozygous, other diseases associated with mutations in the ABCB4 gene\(^{[6,15-18]}\), such as ICP, cholelithiasis, drug-induced intrahepatic cholestasis, and primary biliary cirrhosis,
Copper accumulation may also be seen in primary biliary cirrhosis, primary sclerosing cholangitis, secondary sclerosing cholangitis, biliary atresia, prolonged extrahepatic biliary obstruction, and in the livers of some normal neonates. The differential diagnosis of these cholestatic liver diseases depends on the corresponding immunological antibody detection and imaging examination.

In conclusion, we made a definitive diagnosis of PFIC3 in a 32-year-old woman based on clinical symptoms, pathological findings, and gene mutation detection. She was treated with ursodeoxycholic acid, and her symptoms and liver function improved after 3 mo. We reported a new mutant gene fragment of PFIC-3, which has not been previously reported in the East Asian population.

ARTICLE HIGHLIGHTS

Case characteristics
The female patient was admitted to our hospital with fatigue, jaundice, and a recently elevated γ-glutamyl transpeptidase (GGT) level.

Clinical diagnosis
The patient had a history of acute hepatitis at age 9 years and was diagnosed as having intrahepatic cholestasis of pregnancy in 2008.

Differential diagnosis
Viral hepatitis (A-E), Epstein-Barr virus, cytomegalovirus infections, and other chronic cholestatic diseases were ruled out.

Laboratory diagnosis
High serum total bilirubin level was repeatedly observed, whereas alkaline phosphatase and GGT were also repeatedly increased and remained at 5-10 times the upper limit of normal.

Imaging diagnosis
Genetic testing revealed a pathogenic heterozygous mutation, ex13 c.1531G > A (p.A511T), in the ATP-binding cassette, subfamily B, member 4 (ABCB4) gene.

Pathological diagnosis
Liver biopsy led to the diagnosis of biliary cirrhosis with ductopenia.

Treatment
The patient’s symptoms and liver function improved after 3 mo of treatment with ursodeoxycholic acid.

Related reports
Reports on progressive familial intrahepatic cholestasis type 3 (PFIC3) with high GGT are rare. We identified a mutant gene fragment in PFIC3, which has not been previously reported in the East Asian population.

Term explanation
PFIC3 is caused by a mutation in the ABCB4 gene encoding multidrug resistance protein 3.

Experiences and lessons
PFIC3 is a subtype of progressive familial intrahepatic cholestasis that differs from PFIC1 and PFIC2 in that serum GGT is elevated.
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