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CASE REPORT

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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Author contributions: Tan YW, Ji HL, and Lu ZH contributed equally to this work; Tan YW and Ge GH designed the research; Ji HL, Lu ZH, Sun L, Zhou XB and Gong YH collected and analyzed the data, and drafted the manuscript; Lu ZH and Sheng JH performed the liver pathological evaluations; Tan YW and Ji HL wrote and revised the manuscript; all authors have read and approved the final version to be published.

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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

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 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 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 γ-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 μmol/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 μmol/L, direct bilirubin 34.6 μmol/L, serum total protein 64.5 g/L, albumin 37.5 g/L, alanine aminotransferase (ALT) 123 U/L, aspartate aminotransferase 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 × 10^9/L, red blood cells 3.77 × 10^{12}/L, hemoglobin 120 g/L, platelets 67 × 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 μmol/L, ALT 58 U/L, ALP 127 U/L, and GGT 127 U/L.

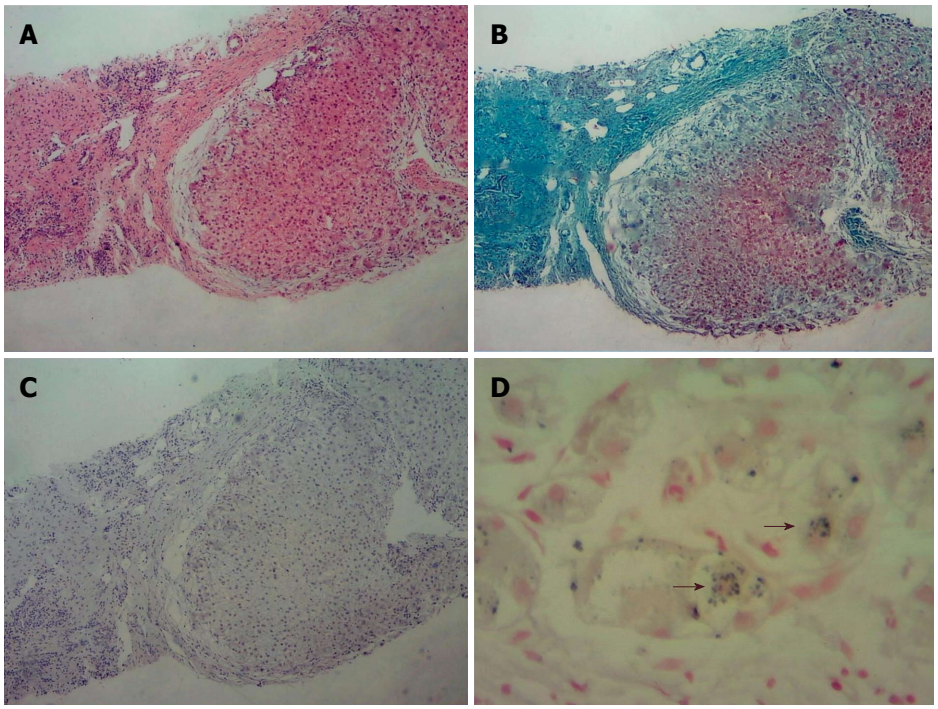

Figure 1 Microscopic features of the liver biopsies. A: Severe fibrosis in the portal area and formation of hepatocyte nodules (hematoxylin and eosin staining, × 100); B: "Halo sign" at the junction of the portal area and liver parenchyma (Masson staining, × 100); C: Ductopenia; immunohistochemical staining for cytokeratin 19 showed no obvious bile duct hyperplasia (CK19 immunohistochemical staining, × 100); D: Hepatocyte cytoplasm showing copper-associated protein sinking (rhodamine staining, × 400).

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 phospholipid 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[8,15-18], such as ICP, cholelithiasis, drug-induced intrahepatic cholestasis, and primary biliary cirrhosis,

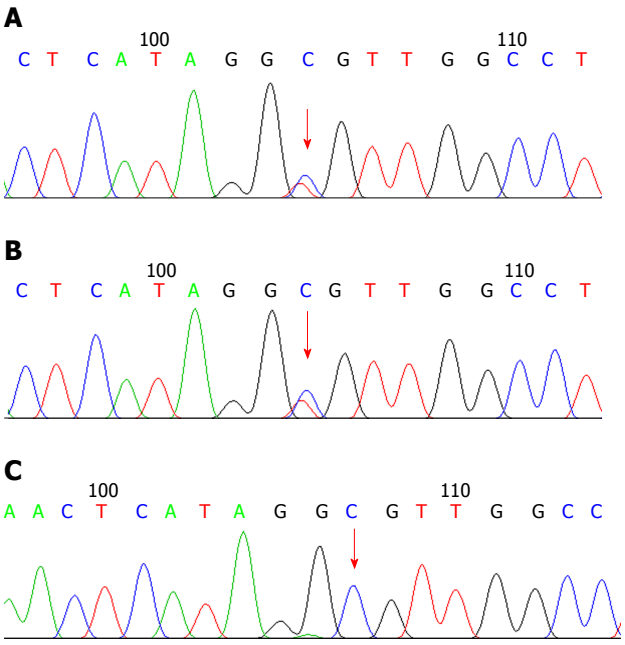

Figure 2 ABCB4_ex13 c.1531G > A (p.A511T) Sanger sequencing map. A: Patient: ABCB4_ex13 c.1531G > A (p.A511T) gene mutation; B: Patient's mother's brother: ABCB4_ex13 c.1531G > A (p.A511T) gene mutation; C: Patient's father: No ABCB4_ex13 c.1531G > A (p.A511T) gene mutation.

often emerge. The most prominent of these presentations are associated with the heterozygous *ABCB4* gene, and can recur multiple times in ICP. The incidence of ICP in patients with PFIC3 is unknown. Gotthardt *et al*[17] found that all pregnant women in a family with the *ABCB4* gene mutation had ICP, suggesting that the *ABCB4* gene mutation is closely related to ICP. Our patient also developed ICP.

Ex13 c.1531G > A (p.A511T) describes a c.1531G > A (p.A511T) heterozygous missense mutation in exon 13 of the *ABCB4* gene, which is included in the Human Gene Mutation Database and has been detected in patients with PFIC3[12]. The frequency of this mutation in the normal East Asian population is 0, and its protein function can be predicted using SIFT (http://sift.jcvi.org/) and Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) software. As the results are all harmful, this mutation is suspected to be disease causing.

The clinical features of PFIC3 may overlap with many other forms of liver disease. In the present case, liver histology showed copper-associated protein sinking in hepatocyte cytoplasm (Figure 1C). Wilson disease (WD) may mimic non-Wilsonian liver disease. The diagnosis of WD should be based on clinical and pathologic parameters as well as genetic testing. Liver biopsy often demonstrates glycogenated nuclei and hepatic steatosis. Typically, there is little or no accumulation of copper. In this patient, WD was finally ruled out because the serum copper level was 90 μg/dL (80-155 μg/dL), the serum ceruloplasmin level was 210 mg/L (200-500 mg/L), no Kayser-Fleischer (K-F) rings were observed, and genetic testing revealed no *ATP7B* mutation.

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-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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