Clinical Case Report

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Biliary atresia combined with progressive familial intrahepatic cholestasis type 3

A case report and review of the literature

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Abstract

Rationale: Neonatal cholestasis is one of the most serious diseases in infancy. Progressive familial intrahepatic cholestasis (PFIC) is a disease that leads to intrahepatic cholestasis. It is one of the common causes of neonatal cholestasis in addition to biliary atresia (BA). The differential diagnosis of neonatal cholestasis is clinically challenging for pediatricians.

Patient concerns: A 4-month-old female presented with severe jaundice, pruritus, and pale stool for 20 days. Abnormally strong echoes near the portal area, an abnormally small gallbladder with an irregularly stiff wall, and splenomegaly were identified on abdominal ultrasound. Blood tests showed elevated alanine aminotransferase, total bilirubin, conjugated bilirubin, gamma-glutamyltranspeptidase, and total bile acid levels.

Diagnosis: Intraoperative cholangiography showed BA. ABCB4 gene mutation IVS13+6G>A/G was confirmed by genetic testing. The patient was diagnosed with BA combined with PFIC3.

Interventions: Kasai portoenterostomy and ursodeoxycholic acid were used for treatment.

Outcomes: Her clinical symptoms and blood tests improved gradually. No recurrence was noted during 1 year of follow-up.

Lessons: Additional examinations, such as genetic testing, should be considered in patients with BA who had refractory jaundice after Kasai portoenterostomy in order to exclude intrahepatic cholestasis.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BA = biliary atresia, CB = conjugated bilirubin, EHBDs = extrahepatic bile ducts, GGT = gamma-glutamyltranspeptidase, PFIC = progressive familial intrahepatic cholestasis, TB = total bilirubin, TBA = total bile acid, UDCA = ursodeoxycholic acid.

Keywords: biliary atresia, cholestasis, Kasai portoenterostomy, PFIC3

1. Introduction

Neonatal cholestasis can be divided into biliary atresia (BA) and non-BA (including progressive familial intrahepatic cholestasis type 3 [PFIC3]). The incidence of neonatal cholestasis is 1 in 2500 live births.[1,2] BA is a disease characterized by dysplasia of the extrahepatic biliary tree. PFIC3 is a rare hepatic disease caused by genetic mutations of ABCB4. Both are sometimes indications for liver transplantation during childhood.[3] Therefore, accurate and timely differential diagnosis and treatment can avoid some life-threatening disorders.[2,4]

BA and PFIC3 are 2 different types of neonatal cholestasis; however, can both occur in the same patient? Here we report a patient whose final diagnosis was BA combined with PFIC3 confirmed by intraoperative cholangiography and gene detection.

2. Case presentation

A 4 months old, Han Chinese female presented to our department with the chief complaints of severe jaundice, pruritus, and pale stool. She had been treated with phototherapy for 2 weeks due to "neonatal jaundice". Twenty days prior to presentation, the jaundice relapsed. She was transferred to our hospital due to severe liver malfunction.

The patient had a history of full-term birth. Her birth weight was 3.25 kg. She had no relevant family history of liver disease. Physical examination revealed jaundice, hepatomegaly, and scratches on her skin. Initial laboratory evaluation showed elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), conjugated bilirubin (CB), gamma-glutamyltranspeptidase (GGT), and total bile acid (TBA) levels and decreased albumin (ALB) level. Serology testing for hepatitis B and C was negative (Table 1).

An obscured gallbladder was detected on magnetic resonance cholangiopancreatography (MRCP). Abdominal ultrasound showed inhomogeneous echoes in the liver and abnormally strong echoes near the portal area. An abnormally small gallbladder with an irregularly stiff wall, and splenomegaly were also shown. A drainage tube was placed; location of the end of the drainage tube was confirmed in the lower duodenum

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Table 1

The patient's liver function before and after operation and oral medication.

	Pre-operation	3 days post-operation	2 weeks post-operation, pre-oral medication	2 months post-oral medication	Normal range
ALT* (U/L)	85	64	126	56	≤33
AST† (U/L)	158	84	148	97	≤32
ALB‡ (g/L)	39.9	28.4	39.6	31.7	38–54
TB§ (μmol/L)	166.8	109.9	207.3	38.5	≤21
CB‖ (μmol/L)	121.3	92.2	172.7	29.5	≤8.0
GGT¶ (U/L)	833	522	484	230	6–42
TBA# (μmol/L)	156.7	143	191	10	≤10.0

* Alanine aminotransferase.
† Aspartate aminotransferase.
‡ Albumin.
§ Total bilirubin.
‖ Conjugated bilirubin.
¶ Gamma-glutamyltranspeptidase.
# Total bile acid.

by X-ray. After 24 hours of discontinuous duodenal drainage during which the patient was fed at regular intervals, drainage of the yellow fluid was not resolved. Liver biopsy showed the following: hyperplasia of collagen fibrils and false liver acinus formed with cholestasis and infiltration of chronic inflammatory cells; fibrovascular and small bile duct proliferations with chronic inflammatory cell infiltration were shown in the hepatic hilums (Fig. 1). Based on the above findings, the diagnosis of BA was made.

The patient was transferred to the surgeon for immediate Kasai operation. Intraoperatively, severe hepatic cholestasis and small nodules deposited on the hepatic surface were found. The gallbladder was atrophied and columnar shaped. The extrahepatic biliary ducts showed stripe-like shapes. The diagnosis of BA was confirmed by intraoperative cholangiography.

On the 3rd postoperative day, jaundice was resolved. The patient's stools were light yellow. Liver function indices showed significant improvement (Table 1). Two weeks later, the patient experienced severe jaundice and pruritus again without fever or other symptoms. Blood tests showed a normal white blood cell and C reaction protein level. Increased levels of ALT, AST, TB, CB, GGT, and TBA and a decreased level of ALB were again identified (Table 1).

Since the patient had already undergone Kasai operation, the cause of the refractory jaundice after the exclusion of postoperative cholangitis was unclear. Considering potential non-BA causes of intrahepatic cholestasis, the patient and her parents underwent genetic testing. Results showed that both the patient and her father had the ABCB4 gene mutation IVS13+6G>A/G (Fig. 2, upper), while her mother had the normal loci (Fig. 2, lower). The patient was diagnosed with PFIC3. The patient was then treated with ursodeoxycholic acid (UDCA) at a dose of 30 mg/kg body weight per day. Fat soluble vitamins and reduced glutathione were prescribed as adjuvant therapy. Liver function and clinical symptoms, including pruritus, were assessed 2 months after hospital discharge; she showed no evidence of recurrence (Table 1). No recurrence was noted during 1 year of follow-up.

Written informed consents for the examinations and for publication of the case were obtained from the patient's parents. The study was approved by the institutional ethic committee of the authors' hospital.

3. Discussion

As mentioned above, the final diagnosis of the patient was BA combined with PFIC3. What is the correlation between BA and PFIC3? No such case has been reported in the medical literature.

First, epidemiological investigations showed that the incidence of BA (mainly extrahepatic BA) is 1/8000 to 1/15,000 live

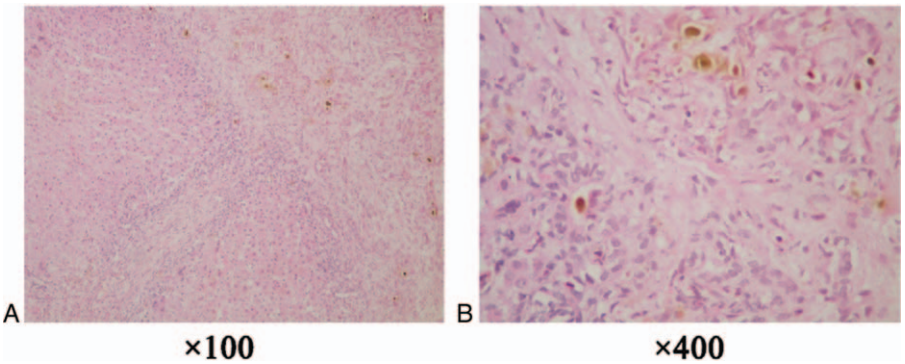

Figure 1. On the left is the 100 times magnified image. On the right is the 400 times magnified image. Liver biopsy examination showed: ① Hyperplasia of collagen fibrils and false liver acinus formed with cholestasis and infiltration of chronic inflammatory cells; ② fibrovascular and small bile duct proliferations with chronic inflammatory cell infiltration were shown in the hepatic hilums.

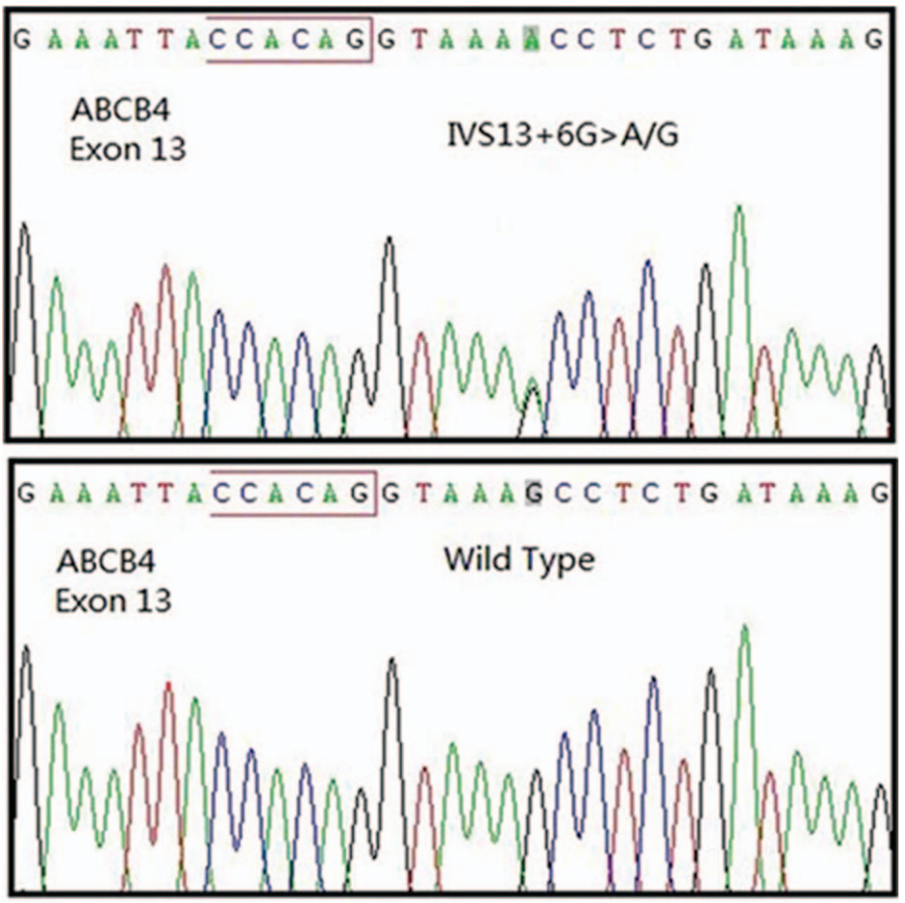

Figure 2. Genetic tests showed that both the patient and her father had the ABCB4 gene mutation IVS13+6G>A/G (Figure 2, upper), while her mother had the normal loci (Figure 2, lower).

births.[2,5] It is the most common cause of neonatal cholestasis worldwide.[6–8] PFIC is considered a rare disease, with an estimated incidence of 1/50,000 to 1/100,000 births. All types of PFIC exist worldwide. Both sexes seem to be equally affected.[9] Hoerning A's retrospective analysis of 82 infants with cholestasis reported that BA account for 41% of cases, while PFIC account for 10% of cases.[10] In our department, 396 patients admitted with neonatal cholestasis were retrospectively analyzed. 178 (45%) were diagnosed with BA. The remaining 218 (55%) were diagnosed with non-BA intrahepatic cholestasis, among whom 3 were diagnosed with PFIC1, 4 with PFIC2, 5 with PFIC3.

Several reports suggest that BA results from prenatal injury and post-inflammatory fibrous obliteration of the extra hepatic biliary tree.[11] It has been found that though the extrahepatic bile ducts (EHBDs) and intrahepatic bile ducts are anatomically near to each other, EHBDs share a common origin with the ventral pancreas but not the liver.[12,13] Sox17, Pdx1, Hes1, HNF6, HNF1β, and Hex factors affect the above process; each of these molecules regulate the extrahepatic bile duct/pancreatic cell fate determination.[14–16] In addition, another theory suggests that dysplasia occurring during embryologic development leads to extrahepatic BA. In Kohsaka's study examining 102 cases of BA, 9 patients had mutated missense Jagged1 gene, suggesting that abnormal Notch signaling may predispose to BA.[17] Studies showed congenital malformations in one-third of BA cases,[18,19] but only 13% of the infants included in Elham Talachian's study had congenital anomalies.[20]

Concerning pathogenesis, PFIC refers to a heterogeneous group of autosomal recessive liver disorders of childhood. Cholestasis of hepatocellular origin often presents in the neonatal period or first year of life and leads to death from liver failure at ages ranging from infancy to adolescence.[21,22] PFIC is divided into 3 types according to gene detection. PFIC4 was proposed by some scholars recently.[23] PFIC1, PFIC2, and PFIC3 are separately caused by mutations of ATP8B1, ABCB11 and ABCB4 genes, respectively, which encode proteins FIC1, BSEP, and MDR3. MRD3 is a phospholipid translocator involved in biliary phospholipid (phosphatidylcholine) excretion and is predominantly, if not exclusively, expressed in the hepatocyte canalicular membrane. [24] The bile salts cannot be inactivated, leading to bile ductule and biliary epithelial cell damage and subsequent intrahepatic cholestasis. The absence of ABCB4 protein is found in patients with severe clinical phenotypes. In cases where the mutated ABCB4 has residual transporter activity, the onset of PFIC3 is later and progression of the disease is slower.[25,26] The differences between PFIC3 and the other types is that serum GGT activity is much higher and, ductular proliferation is noticeable. In addition, the serum primary bile acid concentration is not as high as that seen in the other types of PFIC.[9]

Based on the above analysis, there seems to be no evidence supporting an association between BA and PFIC3. Further study is needed to confirm whether the ABCB4 gene mutation predisposes to BA, as the Jagged1 gene was found to do in Kohsaka's study.[17]

Clinically, the most common symptoms of BA are jaundice, pale stool, dark urine, hepatomegaly and splenomegaly presenting at or shortly after birth.[27,28] Liver histopathology is one of the most important examination methods to diagnose BA; histologic analysis shows bile duct proliferation, bile plugs, edema, and fibrosis of the porta hepatis with preservation of the basic hepatic lobular architecture.[29] Intraoperative cholangiography remains the gold standard for the diagnosis of BA.[30] The first symptoms of PFIC3 are jaundice, hepatomegaly, splenomegaly, and pruritus, which appear in patients as early as 1 month after birth or up to 20 years of age.[31] In PFIC3, liver histology shows portal fibrosis, lobular disarray, and true ductular proliferation with a mixed inflammatory infiltrate.[32] PFIC3 should be suspected in children with a clinical history of cholestasis of unknown origin after exclusion of other primary causes of cholestasis. It can be definitely diagnosed by liver biopsy, analysis of bile, and genetic testing.

As previously mentioned, BA and PFIC3 have different pathomechanisms; thus, different therapy methods should be used.

Kasai portoenterostomy is the most important treatment for extrahepatic BA. It restores bile flow, prevents biliary cirrhosis, and prevents or delays liver transplantation.[33] The operation sets a high demand for early diagnosis. More than 80% of patients with extrahepatic BA who undergo Kasai portoenterostomy before the 60th day of life become jaundice-free, as compared to 20% to 35% of patients who are surgically treated later. In cases with successful biliary drainage, a 15-year survival rate of 87% has been shown.[34] In addition to Kasai portoenterostomy, other auxiliary treatments such as vitamin supplement, glutathlone, and liver transplantation when necessary are also important.

It is noteworthy that UDCA is not recommended as treatment for extrahepatic BA unless the operation is completed. In contrast, treatment with UDCA should be considered in the initial therapeutic management of PFIC3.[1] If UDCA treatment fails, liver transplantation is the only alternative.[33] It is reported that in half of patients, the disease progresses to liver failure, and liver transplantation is required at a mean age of 7.5 years.[21,35–37] In the future, therapies such as cell, gene, or specific targeted pharmacological therapies might represent an alternative approach.[38]

BA and PFIC3 have overlapping clinical features and diagnostic findings. PFIC3 can be diagnosed based on late onset, histopathologic features, and genetic testing. In the current case, the patient was diagnosed with BA definitely based on intraoperative cholangiography. However, jaundice relapsed after Kasai portoenterostomy. After the exclusion of postoperative cholangitis and jaundice, other diagnoses should be considered. Later, targeted treatment for PFIC3 with UDCA was effective.

This case demonstrates that though BA and non-BA intrahepatic cholestasis are 2 different causes of cholestasis, they can present simultaneously. We report this case to demonstrate the circuitous diagnostic process, successful treatment regimen, and the rare diagnosis of BA combined with PFIC3. Though this combination of diagnosis is uncommon, this case presents our valuable experience and beneficial lessons.

First, the patient presented to hospital with chief complaints of severe jaundice, pruritus, and pale stool. It should be recognized that pruritus is one of the most important symptoms of some causes of non-BA intrahepatic cholestasis, especially PFIC3, in addition to BA.[39] In general, PFIC3 has a relative later onset, presenting as early as 1 month after birth or up to 20 years of age,[31] while BA presents early, at or shortly after birth; thus, in our patient, the age of presentation was consistent with both diagnoses.[28] This was the primary cause of misdiagnosis. Therefore, additional examinations should be performed for patients with BA presenting with refractory jaundice after Kasai portoenterostomy in order to exclude intrahepatic cholestasis. Of course, complications such as postoperative cholangitis and jaundice should be excluded. In this case, the diagnosis of BA combined with PFIC3 was confirmed by intraoperative cholangiography and genetic testing. Our patient's clinical symptoms and blood tests improved gradually. No recurrence was noted during the 1-year follow-up period. However, it is not recommended that all patients undergo gene detection early in the course of diagnosis, as genetic causes of cholestasis are rare.

Second, after reviewing the case, what should be improved are as follows:

(1) Since the girl had had liver biopsy before the operation, it could be found that liver lobule was in disarray which was the pathologic features of non-BA intrahepatic cholestasis instead of BA as mentioned above. Some related checks should be taken so as to decrease diagnosis time.
(2) It is reported that the biliary composition of PFIC3 is characterized by normal level of bile salts but decreased phospholipid level. The girl underwent duodenal aspiration but the component cannot be detected other than BA, and so on, in our hospital. The diagnosis time would be decreased if the component could be detected more detail.
(3) It is thought that after the exclusion of complications such as postoperative cholangitis and jaundice, further examination should be made as soon as possible on patients with BA who had refractory jaundice after Kasai portoenterostomy so as to exclude any rare disease.

The third, a larger study is needed to verify the ABCB4 gene mutation rate of BA patients. Also, it is worth studying whether the ABCB4 gene mutation will cause BA besides PFIC3 through influencing the fetal extrahepatic bile duct development or predispose to BA as Jagged1 gene in Kohsaka's study.[17]

4. Conclusions

The case illustrates that additional examinations, such as genetic testing, should be considered in patients with BA who have refractory jaundice after Kasai portoenterostomy in order to exclude intrahepatic cholestasis.

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Author contributions

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Writing – review & editing: Zhi-Hua Huang, Chen Dong.

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