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CASE REPORT – OPEN ACCESS

Progressive Familial Intrahepatic Cholestasis in a Newborn Treated with Liver Transplantation

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ABSTRACT

Background: Progressive familial intrahepatic cholestasis (PFIC) is a severe cholestatic liver disease often requiring a liver transplant (LT). This report describes PFIC in a newborn with jaundice and hepatosplenomegaly treated with LT in the neonatal period.

Case Report: A female infant was referred to the neonatal intensive care unit on the first day of life due to direct hyperbilirubinemia and thrombocytopenia. After excluding other common causes of neonatal cholestatic jaundice in the differential diagnosis and considering the combination of the clinical and laboratory findings of hepatosplenomegaly and biopsy results, the patient was diagnosed with PFIC type 2 (PFIC2). LT was performed on the 33rd day of life once the infant had achieved a weight of 3400 g.

Conclusion: As in this PFIC2 case, PFIC can occasionally be very severe and rapidly progress to liver failure and require liver transplantation in the neonatal period.

Keywords: Cholestasis, liver transplantation, newborn

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INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive inheritance disease that disrupts the genes encoding the protein transporters responsible for bile formation. The disorder has been classified into 3 types (PFIC 1-3) (1). PFIC1 is caused by a mutation of the ATP8B1 gene, which encodes the familial intrahepatic cholestasis 1 (FIC1) protein; PFIC2 by a mutation of the ATP binding cassette subfamily B member 11 (ABCB11) gene, which encodes the bile salt excretion protein; and PFIC3 by a mutation of the ATP binding cassette subfamily B member 4 (ABCB4) gene, which encodes multidrug resistance protein 3 (MDR3) (2).

PFIC2 is the earliest and most severe form, characterized by jaundice, failure to thrive, normal serum gamma-glutamyl transpeptidase (GGT) activity, and elevated serum bile acids appearing in infancy. Hepatic involvement rapidly progresses to cirrhosis with pathological tissue findings of lobular cholestasis, a diffuse giant cell transformation of hepatocytes, and a profound reduction of biliary secretion of bile salts (3). Liver transplantation (LT) is considered a curative treatment for patients with PFIC2 (4).

The present report describes a case of neonatal liver failure due to PFIC2 in a late preterm infant whose symptoms were detected on the first postnatal day and treated with LT at age 33 days.

CASE REPORT

A female infant was referred to a neonatal intensive care unit on the first day of life due to direct hyperbilirubinemia and thrombocytopenia. She was delivered at 36 weeks of gestation by emergency caesarean section due to fetal distress weighing 2.25 kg. There was no consanguinity in the parents and there was no family history of cholestatic liver disease.

A physical examination revealed a weight in the 10th percentile and a length and head circumference in the 3rd percentile. There were no dysmorphic features. Her skin was icteric. She was tachypneic and had hepatosplenomegaly detected at 5 cm from the costal margin but no ascites. Initial blood test results obtained on the first day of life showed thrombocytopenia, with a platelet count of 80000/mm^3, a hemoglobin value of 17.70 g/dL, a total white blood cell count of 8960/mm^3, and a neutrophil count of 4130/mm^3. Liver function tests were normal. The total and conjugated bilirubin values were 9.14 mg/dL and 5.69 mg/dL, respectively. The clotting profile was mildly deranged.

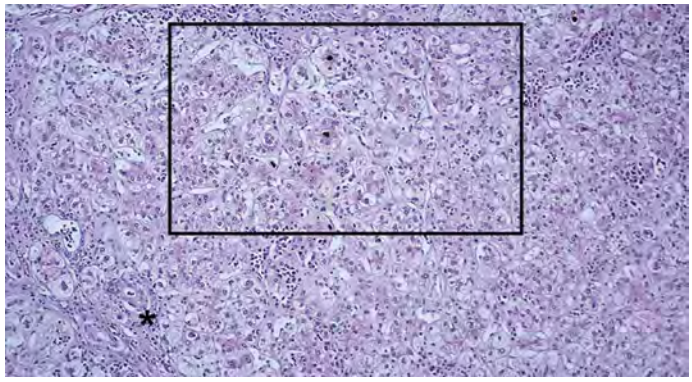

Figure 1. Disorganization seen in the liver with increased connective tissue and limited cholangiolar proliferation in the portal area (asterisk) accompanied by inflammation, pseudoacinar structures, bile plugs, and cell loss in the lobule (H&E, x100)

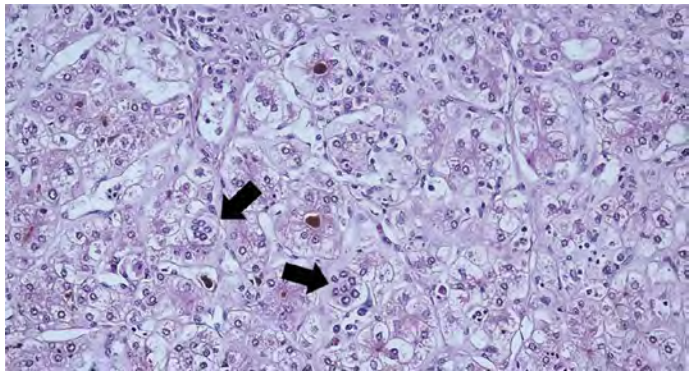

Figure 2. Greater magnification of the area inside the rectangle in Figure 1 demonstrating cholestasis, giant cells (arrows), and inflammation (H&E, x200)

Serological tests for hepatitis A, B, C, toxoplasma, rubella, cytomegalovirus, syphilis, and herpes simplex virus were all negative. No abnormal elevation of organic acids in the urine was detected. Tandem mass spectrometry results and the alpha-1-antitrypsin level were normal. The total bile acid levels were elevated, while the serum ferritin level and iron profile were normal. An ophthalmoscopic examination was unremarkable. An ultrasonogram of the hepatobiliary system showed mild hepatosplenomegaly with a well-visualized gall bladder.

After excluding other common causes of neonatal cholestatic jaundice in the differential diagnosis and considering all of the clinical findings of hepatosplenomegaly with direct hyperbilirubinemia, normal GGT levels, and high total bile acid levels, the infant was diagnosed with PFIC, probably PFIC2, due to the severe early postnatal clinical and laboratory findings detected.

Supportive medical treatment was applied. A liver biopsy was performed on 11th day of life. In the hepatectomy specimen, the normal structure demonstrated a micronodular retention rate of indocyanine green in structures <3 mm. Microscopic examination of tissue samples revealed disorganization with fibrosis in both the portal and centrilobular areas, the formation of a small number of micronodules, canalicular and hepatocellular cholestasis in acinar structures, hepatocellular necrosis, and lobular inflammation and giant cells consistent with PFIC2 (Fig. 1, 2).

The patient's condition deteriorated after 2 weeks of life. Her respiratory difficulty increased due to a grossly distended abdomen and she was intubated on day 17. Progressive hepatic dysfunction with severe coagulopathy, hypoalbuminemia, ascites, and renal impairment appeared. The pediatric gastroenterology team decided that a liver transplant was necessary.

A living donor LT was performed on the 33rd day of life once she had achieved a weight of 3400 g. A laparotomy revealed massive ascites and the graft was cirrhotic. Tacrolimus and methylprednisolone were administered for immunosuppression. Fat-soluble vitamins were injected. Ursodeoxycholic acid treatment was implemented after the transplantation. Follow-up was performed for complications, such as viral infection, rejection, hepatic vein or biliary stenosis, and none were observed. The serum tacrolimus and liver enzyme levels were evaluated intermittently. The tacrolimus dose was adjusted to serum level. The infant was extubated on the 58th day of life and discharged on the 80th day with a plan for tacrolimus treatment and valganciclovir prophylaxis. Breastfeeding was initiated and adequate weight gain was observed. The jaundice and hepatosplenomegaly were seen to regress during outpatient follow-up, and the liver enzymes and coagulation values continued to be within normal limits. In the fourth month after the transplant, respiratory and circulatory failure developed due to aspiration at home. The patient died in the pediatric intensive care unit to which she was referred.

DISCUSSION

PFIC is an unusual cause of neonatal cholestasis (3). The disease occurs due to a defect in bile acid transport, leading to cholestasis, and results in hepatocellular injury (5). The diagnosis of PFIC1 and PFIC2, which appear early in life, are primarily based on clinical and laboratory findings (6). Low-to-normal serum GGT activity, despite conjugated hyperbilirubinemia, is the hallmark of PFIC1 and PFIC2, as GGT activity is elevated in most other types of cholestasis (6, 7). However, there are also some distinct differences between the PFIC1 and PFIC subtypes. PFIC2 tends to present in the neonatal period and progress more rapidly. Our patient had hepatosplenomegaly and jaundice that was noticeable on the first day of life. The direct bilirubin levels gradually increased, whereas the aspartate transaminase, alanine transaminase, and GGT levels were within the normal range. The disease progressed to liver failure within 1 month, which suggested PFIC2 disease.

A liver biopsy also reveals histological differences between the subtypes. Early on in the disease, patients with PFIC2 may present with neonatal giant cell hepatitis and lobular inflammation; however, there can be rapid progression with prominent duct reaction and progression to cirrhosis. In PFIC1 patients, fibrosis progresses in the absence of significant inflammation and ductular reaction. Our patient had centrilobular cholestasis, giant cell hepatitis, portal fibrosis, and portal inflammation according to the liver biopsy findings, which was more consistent with the pathological findings of PFIC2 (6, 7).

Detecting the mutations that disrupt the genes encoding protein transporters, which are responsible for bile formation, is important in the differentiation of PFIC subtypes (7). Unfortunately, in

this case we were unable to obtain genetic tests as they were not performed in our hospital and the high cost prohibited the parents from paying for them to be performed in another laboratory. However, we suggest that the diagnosis of PFIC2 disease should be accepted on the basis of the clinical, laboratory, and histopathological findings (7). To our knowledge, this is one of the most severe cases of PFIC2 to be reported in literature, with the detection of hepatosplenomegaly and cholestasis on the first day of life and progressing to liver failure within 1 month.

Orthotopic LT from a living donor can be an option when medical treatment has failed, and early transplantation in PFIC2 appears to be warranted, as this subtype seems to progress to cirrhosis faster (6). The present case is also one of the earliest cases in the literature of LT due to cirrhosis when compared with other PFIC patients.

In conclusion, PFIC is generally characterized by progressive biliary cirrhosis and hepatic failure in the first or second decade, however, rarely, it can be very severe and rapidly progress to liver failure, as in our PFIC2 case, and require LT in the neonatal period.

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