Cholestasis After Pediatric Liver Transplantation–Recurrence of a Progressive Familial Intrahepatic Cholestasis Phenotype as a Rare Differential Diagnosis: A Case Report

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ABSTRACT

Introduction. Nonobstructive cholestasis after pediatric liver transplantation is a common diagnostic and therapeutic dilemma. We describe a girl with neonatal cholestasis because of progressive familial intrahepatic cholestasis 2 (PFIC-2) and presence of a homozygous splice site mutation in the ABCB11 gene. Liver transplantation was performed because of end-stage liver disease at the age of 6. Cholestasis with normal gamma-glutamyl transferase (GGT) developed 8 years after liver transplantation. A liver biopsy showed canalicular cholestasis and giant cell hepatitis without evidence of rejection, mimicking PFIC-2. Immunofluorescence staining of normal human liver sections with patient's serum revealed reactivity toward a canalicular epitope, which could be identified as bile salt export pump (BSEP) using BSEP–yellow fluorescent protein (YFP) transfected cells. Our patient developed a recurrence of a PFIC-2 phenotype due to production of antibodies against BSEP (alloimmune BSEP disease [AIBD]). Intensification of immunosuppressive therapy as well as antibody treatment with plasmapheresis and Rituximab were initiated, leading to stabilization of the clinical condition and depletion of anti-BSEP antibodies in serum. However, after 1 year liver transplantation was necessary again because of end-stage liver insufficiency. Afterward, immunomodulatory treatment consisted of tacrolimus, mycophenolate mofetil, prednisone, immunoadsorption, and high-dose immunoglobulin therapy (1 g/kg/d).

Conclusion. Cholestasis after liver transplantation may indicate an AIBD with a PFIC-2 phenotype. Besides enhancement of immunosuppressive therapy, an antibody depletion with plasmapheresis, immunoadsorption, immunoglobulins, and B-cell depletion represents a therapeutic option.

THE PROGRESSIVE familial intrahepatic cholestasis (PFIC) is classified in six subtypes (PFIC 1–6). PFIC-2 is an autosomal recessive disorder that is caused by mutations in the ABCB11 (ATP-binding cassette [ABC] family B member 11) gene encoding bile salt export pump (BSEP) located on chromosome 2 (2q24) [1–7]. BSEP is exclusively expressed in the sinusoidal membrane of hepatocytes and is responsible for bile salt secretion into the biliary system, thus liver transplantation is regarded as curative treatment [8,9]. PFIC-2 is characterized by infancy onset of icterus with severe pruritus and failure to thrive, persistently normal or only slightly elevated serum gamma-glutamyl transferase (GGT) activity, elevated serum bile acids, lobular cholestasis with a diffuse giant cell transformation of

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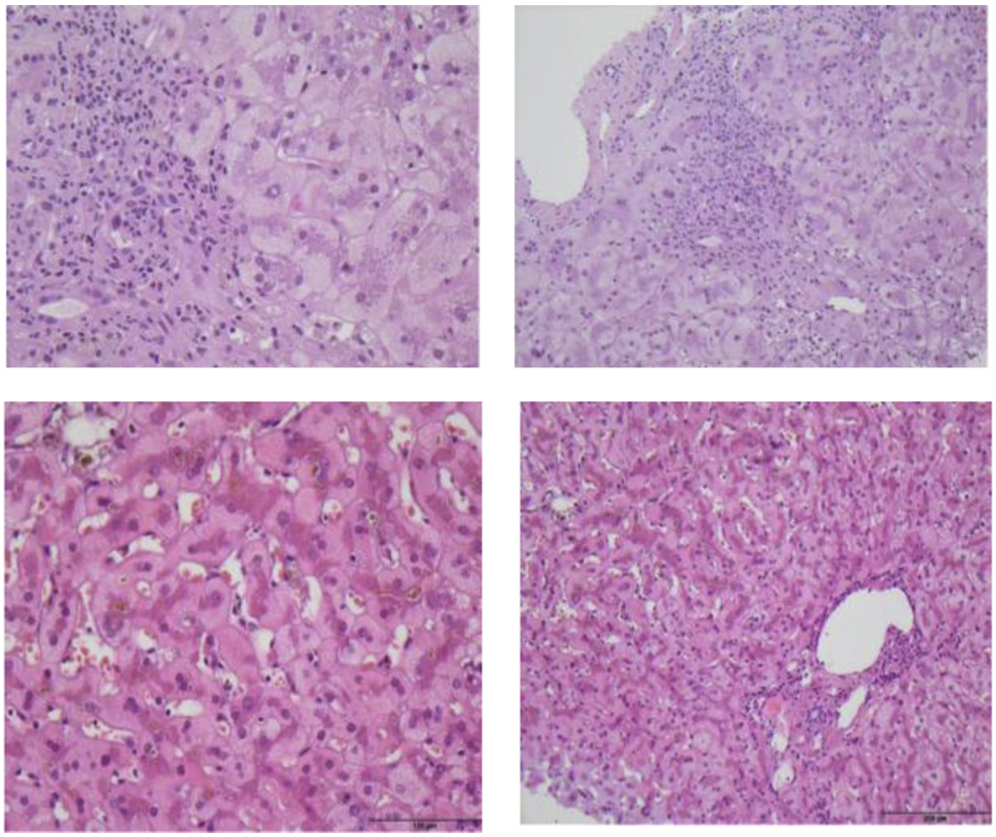

Fig 1. Pictures of liver biopsy specimens: typical pathological changes of PFIC are recognizable. Despite intensive therapy, hepatic fibrosis and inflammation increase over time. (**Top**) Histological findings of liver biopsy from February 2015. Increase of portal fibrosis and portal inflammation with giant cell hepatitis. Left, original magnification x400; right, original magnification x200. (**Bottom**) Histological findings of liver biopsy from December 2014. Canalicular choleastasis and giant cell hepatitis are recognizable. Left, original magnification x200; right, original magnification x400.

hepatocytes, absence of canalicular BSEP staining, and profound reduction of biliary secretion of bile salts [2,3,10,11]. This cholestatic liver disease may be refractory to medical and surgical management and progresses to its end stage often within the first decade of life. So far, liver transplantation (LTX) has been considered curative for patients with PFIC type 2 because BSEP has no function outside the liver [1,10,12]. During the past 7 years, several pediatric patients, who successfully underwent transplantation for PFIC-2, were reported to develop cholestasis with the histological and biochemical features of primary BSEP deficiency and new appearance of anti-BSEP antibodies, thus termed alloimmune BSEP disease (AIBD) [13–15]. To date, several therapy options, including increase of immunosuppressive treatment, plasmapheresis, immunoadsorption, and B-cell depletion (rituximab), were considered to be effective to achieve remission of anti-BSEP disease [13–19]. We report on a girl with cholestasis and icterus after LTX because of recurrence of PFIC-2 phenotype, whose diagnosis and treatment for depletion of anti-BSEP antibodies demonstrated the complexity of AIBD.

METHODS

Detection of anti-BSEP Antibodies

Liver biopsy specimen was analyzed by immunohistochemistry using MRP2 antibodies and respective FITC-labelled secondary antibodies as well as a Cy-3–labelled antibody directed against human immunoglobulin G (IgG). After detection of canalicular antibody deposition, suggesting the presence of anti-BSEP antibodies, further serum immunofluorescence analysis was performed. Human Embryonic Kidney 293 (HEK293) cells were transiently transfected with a complementary DNA (cDNA) encoding BSEP tagged with yellow fluorescent protein (YFP). Fixed cells were stained with the patient's serum in different dilutions as primary antibody and with the Cy-3–labelled anti-human IgG antibody as secondary antibody. Western blotting using cell lysates of BSEP-expressing cells and the patient's serum as primary antibody was used to verify the results from immunofluorescence. Anti-BSEP antibody titers were determined by dilution of the patient's serum and staining of control human liver slices as described [14,20].

CASE REPORT

We report a teenager with history of neonatal cholestasis because of PFIC-2. Diagnosis was confirmed by detection of a homozygous