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Short Communication

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Successful Use of Bortezomib for Recurrent Progressive Familial Intrahepatic Cholestasis Type II After Liver Transplantation: A Pediatric Case with a 9-Year Follow-Up

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ABSTRACT

Recurrence of progressive familial intrahepatic cholestasis (PFIC) type II poses challenges during postoperative liver transplant care. Posttransplant patients with PFIC type II risk developing recurrent cholestasis with normal gamma-glutamyl transferase activity, which mimics the original bile salt export pump (BSEP) protein deficiency and is related to a form of immunoglobulin G antibody (anti-BSEP)-mediated rejection. Bortezomib effectively induces apoptosis of actively antibody-producing plasma cells that may have a role in antibody-mediated rejection. In this case, we used bortezomib to treat PFIC type II recurrence after liver transplantation in a child.

Keywords: Liver transplantation; Bortezomib; PFIC type II; Bile salt export pump deficiency

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) type II (Online Mendelian Inheritance in Man no. 601847) is a severe and refractory condition in neonates caused by mutations in the ATP-binding cassette family B member 11 (*ABCB11*) gene at chromosome 2q24 [1]. The bile salt export pump (BSEP) protein, encoded by *ABCB11*, is expressed in hepatocytes and has a critical role in excreting bile acids. Defective or absent BSEP in PFIC type II results in markedly decreased bile salt secretion from the liver to the gut and bile acid accumulation within the liver, which can lead to toxicity and cholestatic complications, including intractable pruritus, fat-soluble vitamin deficiency, and growth failure [2]. Additionally, PFIC type II rapidly progresses to liver cirrhosis and occasionally liver cancer. In patients with PFIC type II, the diagnosis is confirmed by identifying the *ABCB11* mutation and clinical and histopathologic features such as low gamma-glutamyl transferase (GGT) levels despite cholestasis, loss of BSEP protein expression in immunohistochemical staining, and distinctive findings on electron microscopy of the liver.

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Conflict of Interest
The authors have no financial conflicts of interest.

Treatment for PFIC type II involves standard measures for managing pediatric patients with chronic cholestasis, including correcting vitamin deficiencies, addressing coagulopathy, providing nutritional supplementation with medium-chain triglycerides, and managing pruritus. Pruritus in PFIC type II is generally unresponsive to conventional medical therapies [3] and often leads to insomnia. A new drug, Bylvay (odevixibat), has been shown to reduce pruritus and serum bile acid levels [4]. However, owing to its high cost, it remains unavailable under the Korean National Health Insurance Service system. Given the refractoriness of the disease to medical treatments, liver transplantation remains the only therapeutic option for end-stage PFIC type II in Korea.

Despite the success of pediatric liver transplantation in Korea [5], PFIC type II poses challenges during posttransplant care. Patients with PFIC type II risk developing recurrent normal-GGT cholestasis that mimics the original BSEP deficiency after transplantation [6], which is believed to be related to immunoglobulin G antibody (anti-BSEP)-mediated rejection. Liver biopsies seldom show the typical features of acute cellular rejection in these patients. Unfortunately, PFIC type II recurrence has also been observed during retransplantation and intensified immunosuppressant regimens have only temporarily treated recurrent cholestasis. Consequently, decision-making becomes difficult when considering transplantation or retransplantation for patients with PFIC type II. As this kind of recurrence is viewed as a form of humoral rejection, it has been treated with rituximab in combination with intravenous immunoglobulin and plasmapheresis, achieving remission in some cases [7]. However, cases requiring retransplantation due to only transient improvement have also been reported.

Bortezomib is an anticancer drug for multiple myeloma and mantle cell lymphoma [8]. It is a proteasome inhibitor that interferes with intracellular signaling through nuclear factor-κB, induces apoptosis, and efficiently depletes long-lived plasma cells [9]. Bortezomib has recently been reported as a potential treatment for refractory antibody-mediated rejection in adult recipients of solid organs, primarily the kidney and liver [10,11]. The conventional therapy for humoral rejection is rituximab, a monoclonal antibody against the B-cell marker CD20 [12]. However, theoretically, rituximab cannot deplete plasma cells that produce specific antibodies. Based on this principle, bortezomib has been used to treat antibody-mediated rejection in liver transplant recipients, resulting in improved outcomes in several cases [13]. Here, we report a pediatric case of post-liver transplant PFIC type II recurrence treated with bortezomib and followed up for a long duration.

CASE REPORT

A 10-year-old girl with prolonged cholestasis visited our hospital. At age 1 year, she underwent liver transplantation for PFIC type II at another facility. She had jaundice, abdominal pain, severe pruritus, and recent weight loss (10%). At the time of admission, she was taking the usual doses of tacrolimus and prednisolone for the rejection. On physical examination, her liver was swollen, but the spleen was not firm. Serologic tests revealed aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels of 478/553 IU/L, total bilirubin/direct bilirubin (TB/DB) levels of 20/15 mg/dL, a GGT level of 30 IU/L, and a bile acid level of >150 mg/dL. Computed tomography of the liver revealed homogeneous hepatic enhancement without focal lesions, intact vascular structures, and no gross changes to the intrahepatic bile ducts. Genetic testing confirmed the original diagnosis, identifying a well-known homozygotic nonsense mutation (C.1416T>A; p.Tyr472*).

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A liver biopsy revealed severe canalicular cholestasis and perivenular, perisinusoidal, and periportal fibrosis (**Fig. 1A**). Diffuse loss of BSEP expression in the canalicular membrane was observed in immunohistochemical staining (**Fig. 1B**). In addition, focal C4d deposition was noted around the hepatic arteriole, suggesting recurrent BSEP deficiency after transplant and mild acute cellular rejection. In addition, Epstein–Barr virus viremia was present; however, no virus-positive cells were identified by *in situ* hybridization after liver biopsy, and posttransplant lymphoproliferative disorder lesions were not detected on colonoscopy and positron emission tomography–computed tomography.

During the first 2 months of admission, intensified immunosuppression, including high-dose corticosteroids, was ineffective in controlling cholestasis. Based on reports that recurrence of the original disease after transplant occurs because of the presence of circulating antibodies to BSEP [6,14], an initial treatment regimen consisting of rituximab (375 mg/m^2 body surface area), high-volume plasmapheresis, and intravenous immunoglobulin (2 g/kg) was introduced. However, during the following 2 weeks, laboratory findings did not improve (AST, 293 IU/L; ALT, 192 IU/L; TB, 16.8 mg/dL; DB, 13.5 mg/dL; GGT, 29 IU/L).

The patient subsequently received four doses of bortezomib (1.3 mg/m^2 body surface area; days 0, 4, 8, and 11). Improved laboratory parameters (TB, 4.8 mg/dL; DB, 2.9 mg/dL) were observed 2 weeks after bortezomib administration, and further stabilization of the serologic profile (AST, 135 IU/L; ALT, 146 IU/L; TB, 2.2 mg/dL; DB, 1.1 mg/dL; GGT, 24 IU/L) was noted 2 months later (**Fig. 2**). A follow-up biopsy after 6 months of bortezomib treatment demonstrated complete resolution of the recurrence, supported by a marked increase in BSEP expression compared with a healthy control sample and the absence of C4d expression in immunohistochemical staining.

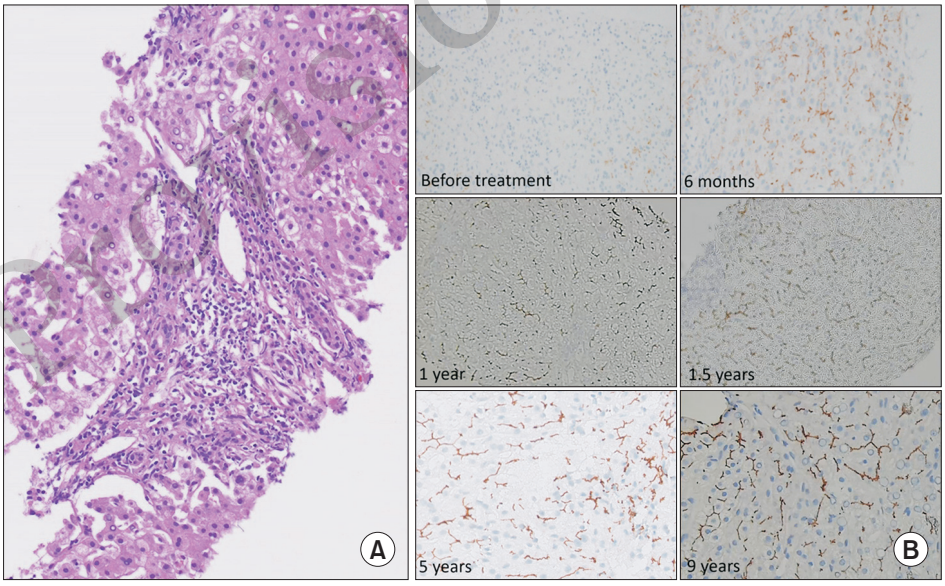

Fig. 1. Histological findings in a patient with persistent cholestasis after liver transplantation. (A) Hematoxylin and eosin staining of the initial liver biopsy specimen. Canalicular cholestasis and perivenular, perisinusoidal, and periportal fibrosis were noted. (B) Immunohistochemical staining for BSEP protein in liver biopsy specimens before and after bortezomib administration. Immunohistochemistry of the initial biopsy specimen showed diffuse loss of BSEP expression in the canalicular membrane. After bortezomib treatment, BSEP expression was rapidly restored and maintained over a long-term period.
BSEP: bile salt export pump.

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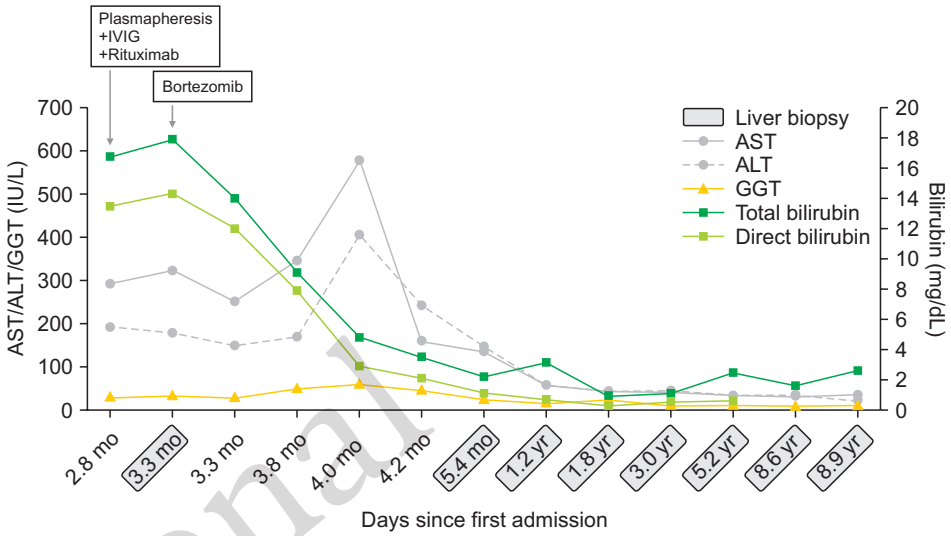

Fig. 2. Illustration of the patient's clinical course. After 2 weeks of bortezomib administration, cholestasis quickly improved. Cholestasis resolution continued after 2 months of treatment.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, IVIG: intravenous immunoglobulin.

Since then, liver biopsies have been routinely performed during the follow-up. After 9 years of bortezomib administration, BSEP expression remains intact (**Fig. 1B**), with stable serology (DB, 0.6 mg/dL; GGT, 24 IU/L; bile acid, 11 mg/dL). Recently, the patient experienced moderate acute cellular rejection, which was successfully treated with intermittent high doses of corticosteroids. During the follow-up period, she did not experience any severe health complications, such as serious infections. Mild Epstein–Barr virus viremia was often detected, but no signs of posttransplant lymphoproliferative disorder were noted. At the time of writing this report, her health condition was good.

DISCUSSION

This case represents the first use of bortezomib for treating BSEP deficiency recurrence after liver transplantation in a child with PFIC type II. The short-term response was rapid and successfully maintained throughout the long-term (9 years) follow-up. Moreover, no critical drug-related complications or relevant health issues occurred during the follow-up. However, we did not test for anti-BSEP antibodies in serology and biopsy specimens, which are the essential and direct indicators of antibody-mediated recurrence. A general profile of humoral rejection, such as panel-reactive and donor-specific antibodies, was not evaluated. Furthermore, rituximab administration and plasmapheresis were performed before and after bortezomib administration, complicating the attribution of results to a specific treatment. Although this was not the intended purpose, this clinical case may represent a multidimensional approach (clearance of antibodies [plasmapheresis], depletion of antibody production [bortezomib], prevention of future antibody production [rituximab], and overall immunosuppression [tacrolimus and corticosteroid]) in the treatment of specific antibody-mediated rejection. While this successful case cannot provide a definitive guideline for treating posttransplant PFIC type II recurrence, we plan to use the same approach in similar cases in the future.

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Kubitz et al. [15] explained that autoimmune BSEP disease develops after liver transplantation because autotolerance to BSEP does not occur in children with PFIC type II. The development of anti-BSEP antibodies often leads to retransplantation [14,15] primarily because it is often refractory to immunosuppressive therapy focused on T-cell-mediated rejection (e.g., combined treatment with cyclosporine, prednisone, and azathioprine or changes to tacrolimus, prednisolone, and mycophenolate mofetil). In our case, we initially performed intravenous immunoglobulin, plasmapheresis, and rituximab treatment to remove anti-BSEP antibodies; however, this did not provide immediate improvement. These treatments can be effective in depleting immature B cells, but they are not effective against antibody-producing cells [10]. Rituximab, intravenous immunoglobulin, and plasmapheresis have been used effectively [16]. However, when these methods are not effective for disease recurrence, leading to cholestasis and damage to the transplanted liver, retransplantation may be needed.

Bortezomib is a drug that inhibits the chymotrypsin-like site of the 20S proteolytic core within the 26S proteasome, leading to plasma cell apoptosis [9,17]. Direct depletion of actively antibody-producing cells by bortezomib may have a role in antibody-mediated rejection. Based on this mechanism, bortezomib has been used not only for common indications such as lymphoma and multiple myeloma but also for antibody-mediated rejection after solid-organ (liver, kidney, or heart) transplantation [10,18,19], desensitization regimens for ABO-incompatible living-donor liver transplantation [20], and steroid-refractory chronic graft-versus-host disease following allogeneic stem cell transplantation. In this case, we noted an immediate response in serum DB levels after initiating bortezomib. Liver biopsy also showed markedly increased expression of BSEP after bortezomib treatment. Notably, bortezomib commonly causes gastrointestinal adverse effects such as diarrhea, nausea, and constipation, as well as hematologic adverse effects such as thrombocytopenia and neutropenia. Moreover, skin rash development has been reported, and patients should be monitored for central nervous system issues such as peripheral neuropathy, fatigue, neuralgia, and headache. Although our patient tolerated bortezomib well without adverse effects, close monitoring is essential when administering this drug.

In conclusion, bortezomib was a safe and effective treatment for posttransplant recurrence of cholestasis with BSEP deficiency in a child with PFIC type II. This case report is limited to a single patient, and further evaluation is needed to confirm the safety and efficacy of bortezomib in pediatric patients. Furthermore, detecting and quantifying anti-BSEP antibodies would be critical in demonstrating the mechanism of the recurrence of BSEP deficiency and assessing the effectiveness of the treatment.

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