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PEDIATRIC LIVER TRANSPLANTATION IN UZBEKISTAN: FIRST CLINICAL CASE AND OUTCOME ANALYSIS

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Background. Liver transplantation (LT) remains the only life-saving option for children with end-stage liver disease. In Uzbekistan, a national LT program was launched in 2018; however, pediatric LT had not been performed until recently. **Objective:** to report the first documented case of related pediatric LT in the Republic of Uzbekistan and to highlight key aspects of postoperative management, including rejection crises, recurrent autoimmune hepatitis (AIH), and the innovative use of bortezomib for treating steroid-resistant rejection. **Materials and methods.** A 15-year-old patient with liver cirrhosis secondary to AIH was selected for transplantation. The right hepatic lobe from a living donor was transplanted following comprehensive preoperative evaluation and preparation. The procedure involved surgical intervention followed by a multistage postoperative treatment protocol. **Results.** The transplant procedure was successful. However, in the early postoperative period, the patient developed a rejection crisis that proved resistant to standard therapy with glucocorticosteroids and antithymocyte globulin. Subsequent evaluation revealed a recurrent AIH. Bortezomib was administered as part of the therapeutic strategy, leading to normalization of laboratory parameters and restoration of graft function. **Conclusion.** This first case of pediatric LT in Uzbekistan demonstrates the feasibility of performing complex surgical interventions and managing challenging postoperative complications. The use of bortezomib for steroid-resistant rejection associated with AIH highlights a potentially promising therapeutic approach. These results mark an important step forward in the development of transplant care in the country.

Keywords: liver transplantation; pediatric liver transplantation; living-related liver transplantation; autoimmune hepatitis; acute transplant rejection; recurrent autoimmune hepatitis; bortezomib.

INTRODUCTION

Liver transplantation has proven to be a life-saving treatment for patients with end-stage liver disease, including pediatric patients [1, 2]. The first pediatric liver transplant (LT) was performed by Thomas Starzl in 1963 on a two-year-old child with biliary atresia [3]. Unfortunately, the patient died from uncontrolled intraoperative bleeding. Following this case, and until the early 1980s, the only technically feasible option for children was orthotopic transplantation of a whole liver from a deceased donor, whose organ size closely matched that of the recipient [4]. However, because of the limited availability of pediatric donors, up to 50% of children on waiting lists died before receiving a transplant [5].

The development of surgical techniques enabling the use of liver segments from adult donors revolutionized pediatric transplantation. A major milestone was the introduction of living donor liver transplantation (LDLT), with the first successful cases in children with biliary atresia reported in 1988 [6, 7]. Over time, related LDLT became a leading approach in many pediatric transplant programs worldwide [1]. In countries where organ donation from deceased donors was prohibited, LDLT remained the only available option [4]. Currently, the outcomes of pediatric LT have improved significantly due to advances in surgical techniques, perioperative management, and rehabilitation approaches [1, 8].

Uzbekistan, a developing country in Central Asia, initiated her LT program in 2018 with the support and direct involvement of Academician Sergey Gautier of the Russian Academy of Sciences. Despite this, notable progress was not achieved until 2021 [9]. By the end of 2023, only one medical center in the country regularly performed liver transplants [10]. Because of legislative restrictions prohibiting the use of organs from deceased donors, only LDLT is currently possible in Uzbekistan [11]. Furthermore, pediatric LT had not been performed in the country until very recently.

This paper presents a clinical observation of a related liver transplant in a child, performed at the National Children's Medical Center in Tashkent, Uzbekistan. To the best of our knowledge, this represents the first documented case of pediatric LT in the Republic of Uzbekistan.

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CLINICAL CASE

This clinical case was approved by the Ethics Committee of the National Children's Medical Center (protocol No. 55-56-24/29.12.2024). The patient's parents provided written informed consent for the use of medical data for scientific research, with full preservation of anonymity.

Examination and preparation for surgery

The 14-year-old boy was admitted to our center in October 2023 with complaints of progressive abdominal distension and blood in his stool. The patient had no history of liver disease or other significant comorbidities. Initial evaluation raised suspicion of chronic liver disease. The patient was referred for comprehensive diagnostic examination in accordance with our center's clinical protocol, including a complete blood count, biochemical profile, coagulation profile tests, and liver ultrasound.

Laboratory tests revealed cytolytic syndrome (ALT 115 U/L, AST 215 U/L), elevated bilirubin levels (63 μmol/L), hypoalbuminemia (28 g/L), and coagulopathy (INR 1.8, prothrombin index 44%, fibrinogen 1.65 g/L). Ultrasonography showed increased hepatic echogenicity, irregular liver contours, hepatosplenomegaly, and ascites.

Given the presence of gastrointestinal bleeding and evidence of portal hypertension, esophagogastroduodenoscopy (EGD) was performed, which revealed grade 3 esophageal varices according to the Paquet classification. Multislice contrast-enhanced computed tomography (MSCT) confirmed cirrhosis, hepatomegaly, splenomegaly, portal hypertension, and ascites.

Considering the endemic situation in Central Asia, viral hepatitis B and C were ruled out. Wilson's disease was also excluded. Autoimmune screening revealed high titers of antinuclear antibodies (ANAs), anti-smooth muscle antibodies (ASMAs), and anti-neutrophil cytoplasmic antibodies (ANCAs). Based on these findings, cirrhosis secondary to AIH (AIH) was diagnosed.

At the initial examination, the patient's MELD score was 20, which served as the basis for recommending LT. At that time, however, there were no pediatric LT programs in Uzbekistan, and the family had limited financial means to afford surgery abroad. Considering these circumstances, along with our team's prior experience in developing LT programs [9], we resolved to initiate a LT program at the National Children's Medical Center.

Preparation for the procedure – including acquisition of essential equipment, specialist training, and patient preparation – took one year. During this period, the patient remained under outpatient observation and received courses of conservative therapy in the hospital whenever his condition worsened. Given the patient's body weight (65 kg) and the presence of portal hypertension, potential donors for right-lobe liver transplantation were assessed, with a required graft-to-recipient weight ratio (GRWR) of at least 1%.

Following the established protocol [11], four potential donors were evaluated: the patient's father, mother, uncle, and aunt. The mother was excluded due to ABO incompatibility, while the uncle and aunt were deemed unsuitable because of hepatitis B infection. The father was identified as a suitable donor, with favorable vascular anatomy and a GRWR of 1.69%. However, his body mass index (BMI) was 34.6 kg/m^2 (106 kg at a height of 175 cm), and elastography revealed grade 2 steatosis. The father was recommended to adjust his diet and exercise. Over the course of a year, he successfully reduced his weight to 83 kg, lowering his BMI to 27.1 kg/m^2; repeat elastography revealed no steatosis.

Upon hospitalization for preoperative preparation in November 2024, the patient's MELD score had risen to 23. In view of coagulopathy, impaired hepatic synthetic function, and erosive changes in the gastric mucosa identified during control EGD, the patient received transfusions of fresh frozen plasma (FFP) and albumin, along with gastroprotective therapy. MSCT confirmed severe portal hypertension, portal vein dilation up to 2.8 cm, and splenomegaly.

Surgery

The surgical technique has been described in detail in our previous reports [9, 11]. The donor underwent right hemihepatectomy, with the surgery lasting for 435 minutes and intraoperative blood loss of 100 ml. The graft weighed 1006 g, corresponding to a GRWR of 1.65%. Primary warm ischemia time was 45 seconds. The graft was implanted into the recipient using the classic technique with complete clamping of the inferior vena cava. Cold ischemia time was 1 hour 35 minutes, and secondary warm ischemia time was 31 minutes. Arterial anastomosis was performed with a continuous twisted suture, and biliary reconstruction was carried out with a Roux-en-Y hepaticojejunostomy and biliary stent placement. The recipient's procedure lasted 665 minutes, with a total blood loss of 800 ml.

Postoperative rehabilitation

In the early postoperative period, the patient remained in the intensive care unit. Planned extubation was performed 8 hours after surgery, but 30 minutes later, the patient developed bronchospasm with oxygen desaturation to 56%, requiring reintubation. A second extubation attempt 3 hours later was successful.

By the end of the second postoperative day, the patient developed postoperative delirium, characterized by motor agitation, obsessive-compulsive behavior, limb tremors, and sleep disturbances. In view of thrombocytopenia and coagulopathy, MSCT and MRI of the brain were performed to rule out organic brain pathology, with

no abnormalities detected. Given the potential neurotoxic effects of tacrolimus, a neurologist recommended anticonvulsant therapy (valproic acid) and haloperidol to treat delirium. Electroencephalogram (EEG) monitoring excluded seizures or latent epileptic activity, leading to discontinuation of anticonvulsants. Delirium resolved only by postoperative day 6, and the patient was transferred to the ward on day 7.

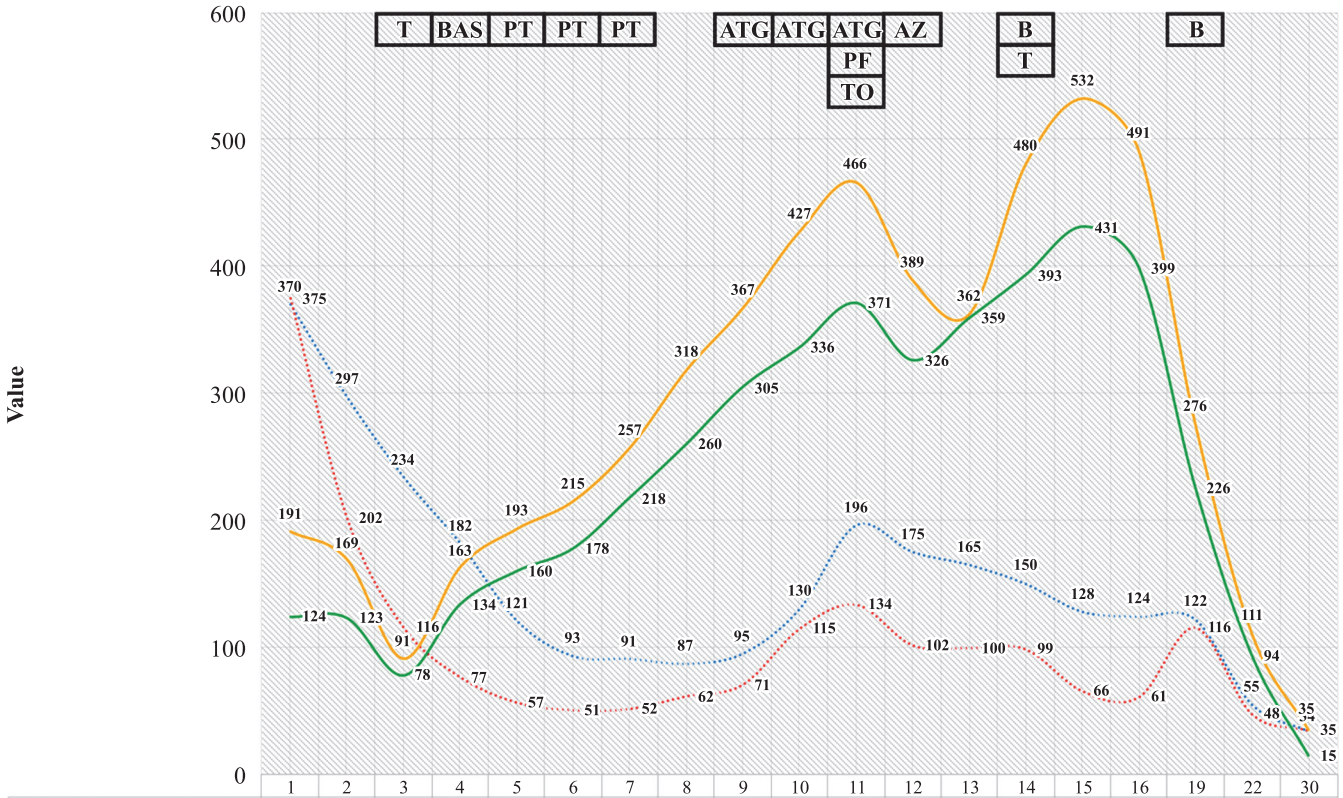
Induction immunosuppressive therapy included basiliximab (days 0 and 4) and methylprednisolone (500 mg) after reperfusion. Tacrolimus was initiated at the end of postoperative day 3. Up to day 4, graft function steadily improved, with declining cytolysis markers and bilirubinemia. From postoperative day 4, however, bilirubin levels began to rise (predominantly direct fraction, Fig.), while cytolysis markers, alkaline phosphatase, and gamma-glutamyl transpeptidase continued to decrease. CMV hepatitis, hepatitis B and C, and biliary and vascular complications were ruled out. Due to thrombocytopenia and coagulopathy, a graft biopsy was not feasible. This increase in bilirubin was empirically attributed to acute rejection, and methylprednisolone pulse therapy (20 mg/kg/day for 3 days) was initiated on day 5, followed by tapering.

The lack of response suggested steroid-resistant rejection, prompting administration of equine antithymocyte globulin (ATG) at 1 mg/kg/day for 3 days. However, ATG was discontinued after the third dose due to severe side effects from ATG (polyneuropathy, headache, hypertension) and lack of therapeutic effect. Despite progressive hyperbilirubinemia, cytolysis and cholestasis markers remained stable.

Toxic liver injury, including tacrolimus-induced hepatotoxicity, was suspected. All potentially hepatotoxic drugs were discontinued, and tacrolimus was switched to azathioprine, but laboratory parameters did not improve.

Screening revealed recurrent AIH, with elevated antinuclear and antineutrophil cytoplasmic antibodies. During this period, the patient also developed progressive cytolytic syndrome (Fig.). A literature review identified several reports on the use of bortezomib for severe immune-mediated conditions [12–19].

The patient underwent plasmapheresis followed by subcutaneous bortezomib at a calculated dose of 1.31 mg/m^2. A sustained positive effect was observed by day 4 after the first dose: bilirubin levels decreased from 532 μmol/L to 276 μmol/L, and liver function normalized. The concomitant elevation of transaminases



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	19	22	30
ALT, U/L	370	297	234	182	121	93	91	87	95	130	196	175	165	150	128	124	122	55	34
AST, U/L	375	202	116	77	57	51	52	62	71	115	134	102	100	99	66	61	116	48	35
Total bilirubin, μmol/L	191	169	91	163	193	215	257	318	367	427	466	389	362	480	532	491	276	111	35
Direct bilirubin, μmol/L	124	123	78	134	160	178	218	260	305	336	371	326	359	393	431	399	226	94	15

Fig. Dynamics of laboratory parameters following living-related liver transplantation under different immunosuppressive regimens. Abbreviations: T, tacrolimus administration; BAS, basiliximab administration; PT, methylprednisolone pulse therapy; ATG, antithymocyte globulin administration; PF, plasmapheresis; TO, tacrolimus discontinuation; AZ, azathioprine administration; B, bortezomib administration

was attributed to tacrolimus toxicity, confirmed by a high plasma level (14.2 ng/dL). Immunosuppressive therapy was subsequently adjusted.

A second dose of bortezomib was administered seven days after the initial administration. By postoperative day 30, the patient's blood counts had fully normalized, and follow-up testing showed no detectable antinuclear or antineutrophil cytoplasmic antibodies.

The postoperative course was uneventful, with no surgical complications. He was discharged under outpatient follow-up. His current immunosuppressive regimen includes tacrolimus, methylprednisolone, and azathioprine.

DISCUSSION

This first successful pediatric LT in Uzbekistan marks a major milestone in the country's transplantation program. Until recently, pediatric LT had not been performed, and this achievement highlights the high level of training, coordination, and professionalism of the multidisciplinary team at the National Children's Medical Center.

What makes this case particularly noteworthy is not only the technical success of the transplantation itself but also the challenging postoperative course. The patient developed a rejection crisis that proved refractory to standard therapy with glucocorticosteroids and ATG, necessitating the use of innovative treatment approaches. The introduction of bortezomib was decisive in stabilizing the patient's condition and preventing graft loss.

Recurrent AIH following LT, although rare, represents a clinically significant complication requiring prompt detection and targeted intervention [12–14]. Literature reports indicate that the risk of post-transplant rejection in patients with AIH can reach up to 65%, while the risk of recurrent AIH is approximately 33% [11, 15, 16].

In this case, reactivation of the autoimmune process manifested as an isolated increase in bilirubin despite stable cytolysis and cholestatic enzyme levels, complicating the diagnostic process. We would like to emphasize that a definitive diagnosis could not be established due to the inability to perform a graft biopsy; however, international protocols support the possibility of diagnosis based on laboratory parameters alone [13], which was applied here.

Several risk factors for recurrent AIH were present in this patient, including young age, the presence of specific HLA alleles (notably HLA-DR3, associated with higher relapse risk), elevated autoantibody titers at the time of transplantation, and an HLA-DR3 mismatch between donor and recipient. Each of these factors is linked to recurrent AIH [12–16].

The use of bortezomib for steroid-resistant rejection and recurrent AIH appears promising, despite limited evidence in the literature [17–19]. Bortezomib, a proteasome inhibitor, induces apoptosis of plasma cells [17] and has been reported in some centers as effective for treating rejection unresponsive to conventional therapy after LT [18]. However, to our knowledge, no prior cases have described its use in pediatric LT. In this case, bortezomib administration resulted in normalization of bilirubin levels and full restoration of graft function.

Importantly, while a peak bilirubin level >461 μmol/L after transplantation is typically considered critical – with graft loss or patient death occurring in more than 95% of cases [20] – our patient, with a peak bilirubin of 532 μmol/L, achieved complete graft recovery. In our prior experience, we reported four cases of early acute rejection after LT [9], two of which were fatal, though none occurred in AIH patients. This case marks the first use of bortezomib in our practice.

The favorable outcome underscores the value of a multidisciplinary approach, involving surgeons, hepatologists, anesthesiologists, immunologists, neurologists, and intensive care specialists. The experience gained during this first pediatric LT in Uzbekistan will contribute to the development of a national transplant program and to improved treatment outcomes for children with end-stage liver disease.

This case highlights important directions for future research: optimizing immunosuppressive regimens, refining monitoring strategies for recurrent autoimmune disease, and defining the role of drugs such as bortezomib in managing post-transplant complications.

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The authors declare no conflict of interest.

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