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Case Report

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COVID-19 In Immediate Postoperative Period of Liver Transplantation and Its Association with Hepatic Artery Thrombosis in A Pediatric Recipient

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) establishes a prothrombotic state. Hepatic artery thrombosis (HAT) after liver transplantation (LT) is a potentially fatal complication.

Case presentation: A 14-year-old girl with negative polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on admission underwent an uneventful LT. Per protocol, unfractionated heparin (UFH) was administered for postoperative anticoagulation, however, anticoagulation goals were not achieved with the usual and even higher doses of UFH. On day 3 post-LT, she developed respiratory distress. On day 5 post-LT, HAT was detected, and thrombectomy and arterial and bile duct re-anastomoses were performed. On day 6 post-LT, the patient had fever. PCR for SARS-CoV-2 was repeated, and the result was positive. On day 27 post-LT, bile leakage that required biliodigestive diversion was observed. Two years post-LT, the patient is asymptomatic, her hepatic artery is patent and her liver enzymes are normal.

Discussion: In this patient, the temporally association of COVID-19 with the impossibility of achieving anticoagulation goals with usual doses of UFH and the development of HAT is striking. It is difficult to determine whether HAT was triggered by the COVID-19-related procoagulant state or whether the patient is one of the few pediatric LT recipients who present with HAT.

Conclusions: Considering the severity of HAT after LT, the current reality of the COVID-19 pandemic, and the changes in coagulation associated with SARS-CoV-2 infection, we deemed it necessary to emphasize the importance of maintaining a strict therapeutic dose of anticoagulation for pediatric LT recipients who develop COVID-19.

Abbreviations: aPPT = activated partial thromboplastin time; ASA = acetylsalicylic acid; COVID-19 = coronavirus disease 2019; DDLT = deceased donor liver transplantation; HAT = hepatic artery thrombosis; HFNC = high-flow nasal cannula; LT = liver transplantation; PCR = polymerase chain reaction; PFIC = progressive familial intrahepatic cholestasis; PICU = pediatric intensive care unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UFH = unfractionated heparin; US = ultrasonography.

Introduction

Patients with coronavirus disease 2019 (COVID-19) develop a prothrombotic state due to significant changes in coagulation [1,2]. Hepatic artery thrombosis (HAT) after liver transplantation (LT) is a serious complication that may jeopardize the integrity of the liver graft and the life of the recipient. The incidence of HAT after LT in pediatric recipients (about 8%) is higher than that in adult patients [3]. Thus, anticoagulation therapy plays an important role in the postoperative period. Several anticoagulation protocols have been published. Unfractionated heparin (UFH) is the most commonly used drug because of its short half-life and the possibility of quickly reversing its anticoagulant effect [4]. The struggle against COVID-19 continues worldwide and there is still a lack of information regarding the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the immediate postoperative period of LT.

Case presentation

A 14-year-old girl with a body weight of 20 kg who had progressive familial intrahepatic cholestasis (PFIC) underwent deceased donor liver transplantation (DDLT) on November 2020, during the first year of the COVID-19 pandemic. The donor was a 6-year-old boy with a body weight of 17 kg, who had been stung by an scorpion 48 hours before. Although he received 3 vials of scorpion antivenom, he ended-up developing refractory status epilepticus and brain death. His peak AST was 32 U/L, ALT 16 U/L and prothrombin time 11.9 seconds. The donor and the recipient had negative polymerase chain reaction (PCR) test results for SARS-CoV-2 on the day of organ recovery and no previous history of respiratory symptoms or recent contact with patients with COVID-19.

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An uneventful DDLT was performed using piggyback technique with duct-to-duct biliary anastomosis. The recipient was not administered any blood products intraoperatively, and after surgery, she was taken to the pediatric intensive care unit (PICU), where COVID-19 restrictions were followed (mandatory use of mask, gown and gloves and visits limited to one parent at a time as long as they had no symptoms). The patient was successfully extubated during the first 2 hours postoperatively. Per institutional protocol, she was started on prostaglandin E1 infusion and UFH, starting at a dose of 10 IU/kg/hour, with dose adjustment based on activated partial thromboplastin time (aPTT) to maintain it at one-and-half to two times over the control value.

Immunosuppressive treatment with Tacrolimus at a dose of 0.1 mg/kg every 12 hours, a steroid regimen based on a pulse of methylprednisolone for five days and a subsequent prednisone taper, and an antibiotic regimen of clindamycin and amikacin were also administered.

As part of graft surveillance, laboratory test and liver Doppler ultrasonography (US) were performed every 24 hours for seven days.

On day 3 post-LT, the patient developed respiratory distress and desaturation of 86%. Thoracic X-ray revealed minimal pleural effusion. We decided on conservative treatment using a high-flow nasal cannula (HFNC) and diuretics, and the patient's response was good. Liver Doppler US performed from day 1 post-LT to day 4 post-LT showed the hepatic artery with adequate flow and resistance indices. In contrast, liver Doppler US performed on day 5 post-LT did not show the hepatic artery; therefore, angiotomography was performed, and it was positive for HAT. Surgical exploration was immediately performed, and it revealed HAT distal to the arterial anastomosis and ischemia of the duct-to-duct biliary anastomosis. Thrombectomy and re-anastomosis of the hepatic artery and bile duct were then performed. The patient was returned to the PICU and administered an infusion of UFH at higher doses, prostaglandins, and acetylsalicylic acid (ASA) at a dose of 100 mg every 48 hours. It is remarkable that in this patient it was necessary to administer a UFH dose of up to 40 IU/kg/hour to achieve the desired aPTT (a dose we had not previously used in 22 years of the program) [Table 1].

On the next day (6 post-LT), the patient developed fever and continued to meet high oxygen requirements using a HFNC. A new PCR test for SARS-CoV-2 was performed, and the result was positive. The coagulation panel revealed a D-dimer level of 11,261 ng/mL, fibrinogen level of 447 mg/dL, C-reactive protein level of 3,600 mg/dL, ferritin level of 183 µg/L, and antithrombin III level of 66%. The patient continued to receive UFH infusion and oxygen supplementation using a HFNC, and the antibiotic administered was changed to a fourth-generation

Table 1. UFH doses and aPTT

Date	Clinical course	aPPT (seconds)	aPPT control value (seconds)	UFH dose (IU/kg/hour)	Anticoagulation therapy goal achieved*
Day 1 pre-LT	**Negative** PCR SARS-CoV-2	28.3	27.8	0	-
Day 0 LT	LT	46.6	27.2	0	-
Day 1 post-LT	-	37.6	27.2	10	**No**
Day 1 post-LT	-	26.7	27.2	10	**No**
Day 1 post-LT	-	28.4	27.8	10	**No**
Day 1 post-LT	-	28.9	27.8	15	**No**
Day 2 post-LT	-	29.4	27.8	20	**No**
Day 2 post-LT	-	37.8	27.7	20	**No**
Day 3 post-LT	Respiratory distress	26.4	27.7	25	**No**
Day 3 post-LT	Sat 86%	20.5	26.9	25	**No**
Day 4 post-LT	-	20.4	27	30	**No**
Day 4 post-LT	-	19.3	27.1	30	**No**
Day 4 post-LT	-	19.7	26.9	30	**No**
Day 5 post-LT	HAT	22.6	27.1	30	**No**
Day 5 post-LT		19.1	26.8	35	**No**
Day 6 post-LT	**Fever, Positive** PCR SARS-CoV-2	44.8	27.2	35	Yes
Day 6 post-LT		27.8	27.3	35	**No**
Day 6 post-LT		48.6	27.3	35	Yes
Day 7 post-LT	-	112.1	27.4	30	Yes
Day 7 post-LT	-	55.2	27	35	Yes
Day 7 post-LT	-	35.7	27.5	40	**No**
Day 8 post-LT	-	35.5	27.8	40	**No**
Day 8 post-LT	-	30.8	26.9	40	**No**
Day 8 post-LT	-	62.7	26.9	35	Yes
Day 8 post-LT	-	58.8	27.2	35	Yes
Day 9 post-LT	-	57.9	27.2	35	Yes
Day 9 post-LT	-	24	27.6	40	**No**
Day 9 post-LT	-	72.4	27.7	35	Yes
Day 10 post-LT	-	53.3	27.7	35	Yes
Day 10 post-LT	-	27.6	27.1	35	**No**

***Anticoagulation therapy goal based on aPTT (i.e., 1.5 to 2 times over control value) was achieved.** UFH, unfractionated heparin; aPTT, activated partial thromboplastin time; LT, liver transplantation; HAT, hepatic artery thrombosis; PCR, polymerase chain reaction; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2

cephalosporin. Post-thrombectomy daily liver Doppler US showed a patent hepatic artery.

On day 8 post-LT, the transaminase levels of the patient increased 8-fold. A steroid pulse was administered for five days, and she responded well to treatment. On day 10 post-LT, UFH infusion was suspended. Anticoagulation with Rivaroxaban was started at a dose of 10 mg/day for 21 days, and ASA was administered at a dose of 50 mg every 48 hours for 3 months. Ten days of antibiotic treatment were completed, and the patient was discharged on day 16 post-LT.

However, on day 24 post-LT, the patient was re-admitted to the hospital with a fever. Abdominal US revealed a patent hepatic artery with good resistance indices, and an intra-abdominal collection was observed. Antibiotic treatment with piperacillin and tazobactam was started. Forty-eight hours later, bile fluid leakage through the surgical wound was observed, and surgical exploration was performed. The surgical exploration revealed bile leakage and a necrotic extrahepatic bile duct, a Roux-en-Y intrahepatic biliodigestive diversion was performed. In the meantime, the patient continued immunosuppression therapy with steroids and Tacrolimus as well as antibiotic treatment (following isolation of *Escherichia coli* sensitive to piperacillin and tazobactam from abdominal fluid). Two transaminase elevation events were recorded and successfully treated with steroid pulse therapy. In addition, the patient had two healthcare-acquired infections, and her response to antibiotic therapy was good. Currently, the patient is asymptomatic, her hepatic artery is patent by US with normal resistance indices and has normal liver enzyme levels at 27 months post-LT.

Discussion

In this report, we present the case of a patient who underwent DDLT secondary to PFIC and, in the immediate post-LT period, developed COVID-19, which was temporally associated with HAT observed on day 5 post-LT. The usual heparin doses used in our LT protocol failed to achieve the expected goals in this patient.

HAT is the most dreaded vascular complication of LT and is the main cause of graft loss. In children, it has a reported incidence of 8.3% and a mortality of 34.3% [3]. In our series of 146 patients who underwent LT, the incidence of HAT is 7.6%. The known risk factors for HAT are technical issues, small vessels, recipient–donor cytomegalovirus mismatch, hypercoagulable states, and prolonged ischemia time [3,5].

The incidence of biliary complications is 10%–35% in pediatric LT [6,7] and 23% in our series, with HAT being a critical factor. Coelho, *et al.* reported that up to 58.7% of patients with HAT have bile duct complications and that 20.4% of patients with bile duct complications have HAT [8].

COVID-19 promotes a prothrombotic state, which has been reported in 25%–50% of patients with severe disease [2,9]. One of the proposed mechanisms of the prothrombotic state is endothelial and vascular injury caused by direct invasion of the endothelium by SARS-CoV-2 [10], resulting in release of pro-inflammatory cytokines (e.g., interleukin-6, interleukin-17A, and tumor necrosis factor-α) secondary to viral infection, increased endothelial damage, and activation of coagulation factors [1,11]. Further, SARS-CoV-2 enters cells at the level of the lungs via angiotensin-converting enzyme 2 receptors, thereby reducing the number of these receptors and increasing the level of angiotensin II, which has vasoconstrictor and procoagulant effects [2]. In addition, decline in the level of antithrombin III, a natural anticoagulant known to have anti-inflammatory effects due to inhibition of nuclear factor-kappa B (NF-κB) has been reported. Thus, in patients with COVID-19, the potential anti-inflammatory effect of antithrombin III is diminished, resulting in increased inflammation, endothelial injury, and cytokine release [9].

In our series, anticoagulant therapy with UFH in the early post-LT period has allowed us to keep a low incidence of HAT (7.6%). Of the 53 LTs performed in the last eight years of the program, this is the first case of HAT we have encountered. Our recipient, did not have any significant known risk factor for HAT (no technical issues, no CMV mismatch D+/R+, no preLT prothrombotic state, total ischemia 8:06 hr, warm ischemia 47 minutes). The temporally association of COVID-19 with the inability to achieve therapeutic effect of UFH with the usual doses and the development of HAT is significant. In patients with COVID-19, some coagulation parameters may change. In their study of 183 patients with COVID-19, Tang, *et al.* reported increase in the D-dimer level, fibrin degradation products, prothrombin time, and aPTT [12]. Resistance to heparin secondary to decrease in antithrombin III level was also reported in another study [13]. The findings of the above-mentioned studies correlate with the high dose of UFH that we had to use in this patient (up to 40 IU/kg/hour) to achieve our therapeutic goal based on aPTT (i.e., one-and-half to two times over baseline value) until day 6 post-LT and after the HAT event.

It has been shown that monitoring of UFH dose based on aPTT may not be accurate because heparin can also bind to other coagulation proteins such as factor VIII, fibrinogen, and other acute phase reactants [14]. Previous studies reported poor concordance between the use of aPTT and anti-Xa level for the monitoring of UFH and that patients with anti-Xa level in the prophylactic range have supratherapeutic aPTT [14,15]. However, one disadvantage of the use of anti-Xa level to monitor the anticoagulant activity of UFH in these patients is that three half-lives of the drug are necessary for accurate levels of anti-Xa to guide the therapy. Therefore, the result would take time, and this delay in the immediate post-LT period is less than ideal for these critical patients [16]. Besides, in our hospital, we do not offer 24-hour measurement of anti-Xa level.

Our patient was admitted urgently so as to receive the liver graft with little or no risk of prolonged ischemia. She had a negative PCR test for SARS-CoV-2 and had no COVID-19 symptoms (mandatory requirements, according to our institute protocol, to be elected as an organ donor or recipient). However, on day 3 post-LT, she had respiratory distress, and three days later, she had fever. PCR test for SARS-CoV-2 was repeated, and a positive result was reported, introducing doubt regarding the time and origin of the infection. Considering that the incubation period of SARS-CoV-2 in most patients is four to five days [17-19], that the highest viral concentration at the level of the pharynx is reached in the fourth or fifth day after symptom onset [20,21], and that the false-negative rate of this test ranges from <5% to 54% [22-25], we posit that the SARS-CoV-2 infection was contracted between day 3 pre-LT and day 3 post-LT.

Transplant programs have been significantly affected by the COVID-19 pandemic. Due to the speed of spread of COVID-19, there is a lack of enough scientific evidence on COVID-19 screening of donors and recipients of liver grafts [26]. However, various recommendations based on epidemiological conditions, clinical factors, and PCR test result for SARS-CoV-2 have been published, with risk classified as high, intermediate, or low [26-28].

We present the case of a pediatric patient who underwent DDLT and developed COVID-19 in the immediate postoperative period. COVID-19 in this patient was found to be temporally associated with HAT

and the impossibility of achieving therapeutic effect of UFH with normal doses. It is difficult to determine whether the HAT was triggered by procoagulant state due to COVID-19 or whether the patient is one of the few pediatric LT recipients (7.6%) who present with HAT. The lack of response to UFH in this patient compels us to pay special attention to anticoagulant management in pediatric LT recipients with COVID-19 .

Conclusions

Considering the severity of HAT after LT, the current reality of the COVID-19 pandemic, and the changes in coagulation associated with SARS-CoV-2 infection, we deemed it necessary to present this case and to emphasize the importance of maintaining a strict anticoagulation therapeutic effect (higher doses of UFH), for pediatric LT recipients who develop COVID-19 in the early post-LT period.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Conflict of Interest

Authors state that they have no relevant conflict of interest.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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