Case Report

COVID-19 infection in a child following liver transplantation

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Summary

COVID-19 infection immediately after liver transplantation presents a unique and challenging situation. In this report, we present the case of an 11-year-old girl who underwent emergency living donor liver transplantation for acute liver failure. After an uneventful intra-operative course, the patient was transferred to the intensive care unit. On the second postoperative day, the patient developed unexplained severe hypoxia. A polymerase chain reaction test was positive for SARS-CoV-2 virus and a hypercoagulable state was indicated by laboratory investigations. Despite therapies such as mechanical ventilation and therapeutic anticoagulation, further clinical deterioration occurred. On the seventh postoperative day, the patient's pupils were fully dilated bilaterally and unreactive to light, and brain death was later confirmed. This report highlights unique challenges pertaining to oxygenation, coagulation and immunosuppression after liver transplantation in a child with COVID-19. Hypoxia of unknown origin in the postoperative period should prompt consideration of COVID-19 as a possible cause.

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Introduction

Acute liver failure is defined as the onset of coagulopathy and encephalopathy within 28 days of the onset of jaundice. It has a mortality of 70–80% without liver transplantation [1]. Liver transplant programmes worldwide have been curtailed by the COVID-19 pandemic, for reasons including reduced clinical capacity and the risk of SARS-CoV-2 infection to an immunosuppressed patient cohort [2]. Case reports of COVID-19 in liver transplant recipients have been presented in the literature [3, 4]. Liu et al report successful treatment of severe COVID-19 pneumonitis in a 50-year-old. In this case, tacrolimus was withheld and low-dose methylprednisolone (40 mg.day^{-1}) was administered [3]. Huang et al describe a case of severe COVID-19 with a fatal outcome in a 59-year-old post-liver transplant patient [4]. The administration of tacrolimus and mycophenolate mofetil was continued at half-dose despite COVID-19 infection, due to suspicion of chronic rejection. However, these reports relate to patients who underwent liver transplantation several years before SARS-CoV-2 infection. COVID-19 immediately after liver transplantation presents a uniquely challenging situation.

Report

A previously well 11-y-old girl weighing 37 kg underwent emergency living donor liver transplantation for acute liver failure of unknown aetiology. Pre-operatively she was sedated and invasively ventilated via a tracheal tube. Clinical examination confirmed grade 4 hepatic encephalopathy with equal pupils sluggishly reacting to light, and computed tomographic imaging

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of the head demonstrated moderate cerebral oedema. Both donor and recipient had negative polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 infection 24 h before transplantation. Intra-operative blood loss was 1700 ml and the surgery was otherwise uneventful. The patient's trachea remained intubated postoperatively and she was transferred to the intensive care unit, receiving fentanyl, propofol and atracurium infusions, plus haemodynamic support comprising noradrenaline 0.3 $\mu g.kg^{-1}.min^{-1}$ and vasopressin 0.5 $IU.h^{-1}$.

On the second postoperative day, the F_IO_2 required to maintain peripheral oxygen saturations greater than 95% gradually increased from 0.4 to 1.0, despite an increase in positive end-expiratory pressure from 5 to 8 cmH_2O. A chest radiograph showed mild bilateral lung infiltrates with blunting of the costophrenic angles and bed-side ultrasound revealed small bilateral pleural effusions. Sputum, urine and blood samples were sent for culture but no organisms were grown. Respiratory swabs were taken for rapid SARS-CoV-2 antigen and RT-PCR testing 36 h after surgery. Both tests returned a positive result. The source of SARS-CoV-2 infection could not be identified despite testing of the child's parents and clinical staff involved in her care.

Hypercoagulability was indicated by a coagulation index of 3.5 (normal range −3 to +3) on thromboelastography (TEG, Haemonetics, Boston, USA) and an increased D-dimer level of 1418 $ng.ml^{-1}$. The patient was therefore commenced on therapeutic anticoagulation (1 $mg.kg^{-1}$ enoxaparin twice daily). Deep venous thrombosis was not observed on bed-side duplex ultrasound screening. A computed tomography pulmonary angiogram was deemed not in the patient's best interests given the risks associated with transfer in the context of high supplementary oxygen requirement and signs of severe cerebral oedema. Prone ventilation was not performed as the patient had undergone recent abdominal surgery.

The patient had received immunosuppressive therapy with methylprednisolone 2 $mg.kg^{-1}$ i.v both intra-operatively and on the first postoperative day. Tacrolimus and mycophenolate mofetil (the usual immunosuppressive agents at our institution) were not commenced postoperatively due to a rising white cell count. Following the diagnosis of COVID-19, hydrocortisone 50 mg i.v was administered three times per day and additional immunosuppressants were withheld.

On the third postoperative day, an improvement in oxygenation was observed with a reduction in F_IO_2 from 1.0 to 0.75. However, platelet count and blood pH began to decline, alongside elevations in lactate, prothrombin time and ammonia levels (Table 1). On the seventh postoperative day, the patient was observed to have dilated pupils non-reactive to light, suggestive of brainstem herniation. The following day, fentanyl, propofol and atracurium infusions were stopped. On the tenth postoperative day the patient was declared brain stem-dead following clinical testing and the absence of electrical activity on electroencephalogram.

Table 1 Peri-operative investigations.

	Pre-operative	Postoperative day							
		0	**1**	**2**	**3**	**5**	**7**	**9**	**10**
Hb $(g.dl^{-1})$	9.2	8	8.3	9.2	9.2	8.6	7.6	7.4	9.6
Leukocytes $(cells.mm^{-3})$	7,900	7,230	10,500	13,500	10,740	10,600	13,900	13,200	42,000
Platelets $(cells.mm^{-3}$ the second)	235	178	223	218	202	114	21	15	14
PT (s) / INR	28/2.6	53/5.21	32/2.9	25/2.3	18/1.6	16/1.5	17/1.5	30/2.79	
Bilirubin $(mg.dl^{-1})$	6.7	9.01	9.11	6.83	7.18	6.34	6.89	11.25	15.23
AST/ALT $(U.l^{-1})$	759/498	490/450	385/413	202/323	163/249	178/192	635/394	3564/1566	5598/3569
ALP/GGT $(U.l^{-1})$	116/20	110/20	116/26	133/35	149/60	136/67	281/109	327/75	665/68
NH3 $(U.dl^{-1})$	379	196	179	176	179	184	227	576	
pH	7.42	7.46	7.49	7.49	7.46	7.42	7.35	7.23	6.9
Lactate $(mmol.l^{-1})$	3.3	2.3	4.4	2.1	2.7	4.7	5.6	11.7	18
PaO_2 (kPa)	32.4	18.8	13.5	11.9	14.9	14.1	15.3	10.2	21.6
$PaCO_2$ (kPa)	5.3	4.6	4.3	5.3	5.2	5.0	5.1	4.8	4.8
F_IO_2	0.4	0.5	0.5	1.0	0.75	0.65	0.5	0.9	0.9

ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate aminotransferase; F_IO_2, Fraction of inspired oxygen; GGT, Gamma-glutamyl transferase; Hb, Haemoglobin; INR, International normalised ratio; NH3, Ammonia; $PaCO_2$, Partial pressure of carbon dioxide in arterial blood; PaO_2, Partial pressure of oxygen in arterial blood; POD, Postoperative day; Pre-op, Pre-operative; PT, Prothrombin time.

Discussion

Infection with SARS-CoV-2 in the immediate post-transplant period in a child with acute liver failure represents a management challenge for the transplant service. The coagulation dynamics after liver transplantation can range from hypo- to hypercoagulable states. As COVID-19 is also a known cause of hypercoagulability [5], both transplantation and COVID-19 may have contributed to the coagulation abnormalities in this case. Hypercoagulability was observed in this patient on postoperative day. All pre- and intra-operative thromboelastography reports were normal.

The clinical team felt that the patient's oxygen requirements were higher than could be explained by chest x-ray and ultrasound findings, prompting repeat testing for SARS-CoV-2 infection, which was positive. COVID-19 can cause endothelial dysfunction and a prothrombotic state by the activation of complement pathways, inflammatory cytokines or by directly penetrating the pulmonary endothelial cells through angiotensin-converting enzyme 2 receptors [6]. In a case series by Ackerman et al, widespread thrombosis with microangiopathy was observed post-mortem in seven patients who had died as a consequence of COVID-19 [7].

Increased D-dimer levels have been associated with poor prognosis in patients with COVID-19 [8]. Previous studies have shown a high incidence of venous thromboembolism despite the use of prophylactic anticoagulation. In this case, we opted to administer therapeutic anticoagulation to treat the hypercoagulable state observed, acknowledging the increased risk of postoperative bleeding.

The risk of stopping immunosuppression after liver transplantation must be weighed against the risk of graft rejection. Therefore, some clinicians recommend reducing the degree of immunosuppression after liver transplantation only in case of severe COVID-19 infection [9]. However, there are no published recommendations on immunosuppression use for COVID-19 infection in the immediate post-transplant period. In this case, COVID-19 was rapidly progressive, based on the sudden increase in supplemental oxygen requirement and it was decided to stop the administration of tacrolimus and mycophenolate mofetil on this basis, while continuing steroid administration.

The fatal outcome in this case was likely multifactorial, including the presence of cerebral oedema pre-operatively and its exacerbation by COVID-19-related hypoxaemia. The delayed resumption of graft function may have resulted in the worsening of cerebral oedema to the point of cerebral herniation.

In conclusion, SARS-CoV-2 infection should be suspected if a patient presents with hypoxia in the postoperative period. This case highlights that COVID-19 shortly after liver transplant in a child with acute liver failure presents unique challenges pertaining to oxygenation, coagulation and immunosuppression. The initiation of therapeutic anticoagulation use must be balanced against the risks of a prothrombotic state and postoperative bleeding. Clinicians should consider modifying the immunosuppression regimen in the transplant patient with COVID-19 given its possible adverse effects in the setting of severe infection and the established benefits of steroid therapy.

Acknowledgements

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