Successful Liver Transplantation in a Patient With Acute COVID-19 Infection and Acute Liver Failure: A Case Report

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Abstract: Current liver transplantation societies recommend recipients with active coronavirus disease 2019 (COVID-19) be deferred from transplantation for at least 2 wks, have symptom resolution and at least 1 negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test.[1] This approach does not address patients who require urgent transplantation and will otherwise die from liver failure. We report a successful orthotopic liver transplant (OLT) in a patient with active COVID-19 infection. This is only the second to be reported worldwide and the first in Canada.

CASE PRESENTATION

A 28-y-old male, previously healthy, was transferred to our institution for possible OLT. He presented 5 d earlier to a community hospital with new onset jaundice and acute liver failure (ALF) of unclear etiology. The history revealed a 1-y duration of heavy alcohol consumption. Work-up was negative for acetaminophen, viral, autoimmune, and infiltrative etiologies. Ultrasound done at the time of admission showed patent vasculature and no cirrhosis. Laboratory investigations completed during his hospitalization are outlined in Table 1. Our patient had 2 negative RT-PCR SARS-CoV-2 tests, 1 at the community hospital on day −22, and 1 the day a SARS-CoV-2 outbreak was reported on the ward to which the patient was admitted, day −14 (using the day of OLT as day 0, see Table 2). His first positive SARS-CoV-2 RT-PCR test occurred 5 d into his admission at our institution.

Three days later (day −9), he deteriorated, developing new onset hepatic encephalopathy and was intubated for altered level of consciousness. Computed tomography of the head did not reveal neuroradiologic findings consistent with COVID-19 or elevated intracranial pressure.[2] COVID-19 infection appeared to be confined to the upper respiratory tract without fever or preceding cough. He was mechanically ventilated with a pressure support of 5 cm H_2O, positive end-expiratory pressure of 5 cm H_2O and FiO_2 30%. Arterial blood gas on these settings showed a Pao_2 of 122 mm Hg and $Paco_2$ of 40 mm Hg. Treatment specific to COVID-19 was not initiated as our patient did not demonstrate pulmonary involvement or hypoxemia.[3] Further hepatic decompensation occurred day −1 with refractory lactic acidosis, hypoglycemia, and hypothermia. Continuous renal replacement therapy was initiated for acute kidney injury and volume overload. His chest x-ray only demonstrated bilateral pleural effusions. Computed tomography of the abdomen revealed large areas of hepatic hypodensity, large volume ascites, but no evidence of thrombosis. His model for end-stage liver disease-sodium score was 47, and Child-Pugh score was 14.

TABLE 1.

Laboratory test results relative to the time of orthotopic liver transplantation

Test	Day −22	Day −12	Day −9	Day −5	Day −1	Day4	Day6	Day 12[a]	Days 26–32	Days 55–58
WBC (× 10⁹/L)	6.1	13.3	12.4	19	9	6.7	6.2	10	11	9.9
Neutrophil count (× 10⁹/L)	3.9	6.7	9.2	15.9	7.5	–	–	–	7.1	6.5
Lymphocyte count (× 10⁹/L)	1.5	3.8	1.2	1.9	0.8	–	–	–	1.8	2.3
Hemoglobin (g/L)	153	164	145	155	93	78	85	87	115	120
Platelet count (× 10⁹/L)	109	125	78	75	46	23	32	124	222	205
Serum lactate (mmol/L)	–	1.7	2.4	6.7[a]	5.3	1.4	–	–	–	–
Serum sodium (mmol/L)	138	139	138	135	140	146	151[a]	139	139	140
Serum creatinine (µmol/L)	80	84	75	157	214	147	124	72	83	86
INR	2.2	2.7	4	4.1	3.3	0.9	1	1	0.9	1
Total bilirubin (µmol/L)	280	408	419	252	378		37	13	8	5
Serum albumin (g/L)	–	27	21		29	25	23	19	35	41
Ammonia (µmol/L)	–	85[a]	184	106[a]	183[a]	–	–	–	–	–
AST (U/L)	1816[a]	743	785	618	291	100	181	113	53	14
ALT (U/L)	2177	1470	1393	915	237	175	308	231	83	18
ALP (U/L)	196[a]	310	245	230	129	94	37	101	93	54
GGT (U/L)	254	293	195	128	26	114	173	159	72	24
C-reactive protein (mg/L)	3.2[a]	4[a]	2.8	6.5	–	–	–	–	–	–
D-dimer (µg/L)	–	766[a]	1181	5632[a]	–	–	–	–	–	
LDH (U/L)	–	413	554	617	494	350	369	321	–	–
Ferritin (µg/L)	–	–	10 259	5535[a]	–	–	–	–	–	–
Procalcitonin (µg/L)	–	–	0.27	–	–	–	–	–	–	–
Tacrolimus level (µg/L)	–	–	–	–	–	6.6	10.6	6.1	6.1	9.1

[a]If result was unavailable, a result within 36 h of that date was used.
"–" signifies no test result available.
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, Gamma-glutamyl transferase; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC, white blood cell count.

TABLE 2.

SARS-CoV-2 test results relative to time of orthotopic liver transplantation

	Day −22	Day −14	Day −12	Day −3	Day −2	Day −1	Day 6	Day 12	Days 26–32	Days 55–58
SARS-CoV-2 RT-PCR (NP)	–	–	+	+	+	+	+	+	+	–
SARS-CoV-2 RT-PCR cycle threshold E gene (NP)[a]			29.5	15.5	18.6	22.1	23.7*	27.5	29.3†	
SARS-CoV-2 RT-PCR cycle threshold RdRP gene (NP)[b]			28.7		18.1			26.8		
SARS-CoV-2 RNA (serum)						+				
COVID-19 total antibody[c]				–		–		+	+	+
COVID-19 IgG antibody[d]				–		–		–	+	+

[a]Cycle threshold values are from laboratory-developed tests for E gene, or commercial test Panther Hologic Fusion* and Roche Cobas†.
[b]Cycle threshold values are from laboratory-developed tests for RNA-dependent RNA polymerase gene.
[c]Commercially available assay (Siemens Total Ab) detects IgA, IgM, and IgG antibodies against spike protein.
[d]Commercially available assay (Abbott Architect) detects IgG against nucleocapsid protein.
"+" indicates a positive result; "–" indicates a negative result.
COVID-19, coronavirus disease 2019; NP, nasopharyngeal swab; RdPR; RNA- dependent RNA polymerase; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The patient underwent a successful OLT 12 d after his initial positive SARS-CoV-2 RT-PCR test. At the time of transplant, he had active COVID-19 infection (Table 2). Intraoperatively, the patient did not demonstrate systemic effects of COVID-19. He required minimal ventilatory support and was hemodynamically stable, transesophageal echocardiography did not demonstrate evidence of ventricular dysfunction, and no evidence of hypercoagulability was noted on rotational thromboelastography.[4,5] Pathology obtained from the explanted liver demonstrated confluent central perivenular and submassive hepatic necrosis, marked cholestasis, preserved portal tracts, and normal vascular structures.

The patient improved rapidly posttransplant. He was extubated day 1, and continuous renal replacement therapy was discontinued. Immunosuppression was induced with corticosteroids. Tacrolimus was initiated on day 1, and mycophenolate mofetil was initiated on day 6. Liver allograft function improved postoperatively (Table 1). Liver biopsy performed day 9 was normal. The patient was discharged on day 15 at which time he had evidence of early antibody response to SARS-CoV-2. Full antibody response was seen 2 wks later (Table 2). By day 55, our patient was no longer positive for SARS-CoV-2 using RT-PCR from a nasopharyngeal sample and had never demonstrated clinical evidence of COVID-19 relapse.

DISCUSSION

No reports of successful OLT in patients with active COVID-19 existed at the time of our decision to proceed with transplantation. Kulkarni et al[6] demonstrated OLT in patients recently (but not acutely) infected with COVID-19. One case report suggested successful OLT during active COVID-19; however, the patient did not have evidence of active infection.[7] We applaud the latest case, similar to ours, which highlights successful OLT in a patient with mild active COVID-19 infection.[8] Although this case report was published after our patient was discharged from hospital, our case adds to existing literature.

Our patient had acute COVID-19 infection at the time of OLT as (a) he was previously RT-PCR negative, (b) RT-PCR cycle threshold was low, (c) no antibodies against SARS-CoV-2 were detectable, and (d) SARS-CoV-2 viral RNA (RNA) was detected in his serum. Viral load (VL) is often reported as cycle threshold (Ct), the time for the amplified viral signal to cross detection threshold; a lower Ct indicates higher VL.[9] Detecting SARS-CoV-2 RNA in serum is common when the VL detected on nasopharyngeal swab is high.[10] The absence of antibodies to SARS-CoV-2 provided further evidence of active COVID-19. Antibodies to SARS-CoV-2 form as early as 4 d from the onset of infection, with 50% and 90% of patients seroconverting at 7 d and 3 wks, respectively.[11,12]

Initial hepatic decompensation in this patient was not from COVID-19; his ALF and biochemical deterioration preceded COVID-19 infection. Although the initial cause of ALF remains unknown, the explanted liver suggested potential drug or toxin-induced injury. A secondary cause for further hepatic decompensation during the patient's admission, however, was possible.[13] Concern existed if decompensation was COVID-19 related, potential multisystem involvement may occur following transplantation. COVID-19 can cause liver injury, but it is typically mild with minimal impairment in synthetic function.[14-17] We cannot rule out that COVID-19 infection did not contribute to further decompensation during hospital admission; however, imaging and pathology from the explanted liver did not demonstrate features consistent with COVID-19-related liver injury.[14,18,19]

Following a multidisciplinary discussion, we proceeded with OLT based on the patient's young age and mild COVID-19 disease, which appeared isolated to the upper respiratory tract. He had limited risk factors for adverse outcome from COVID-19 infection according to data extrapolated from the general population, operative patients or liver transplant recipients (LTR).[20-24] In fact, LTR have lower mortality from COVID-19 than the general population and earlier time because transplant or immunosuppression does not correlate with worse outcome.[21,22] We explored the association between VL, Ct from respiratory secretions or presence of serum SARS-CoV-2 RNA (RNA-emia), and disease severity in COVID-19. RNA-emia has a stronger association with mortality and disease severity than respiratory tract VL or Ct.[10,25,26] However, RNA-emia and respiratory tract VL have only been shown to predict adverse outcome in patients with COVID-19 that require hospitalization.[10,25,26] The presence of high VL and RNA-emia in our patient were of uncertain consequence given that his hospitalization was driven by ALF, not respiratory symptoms. Although low Ct values are associated with positive viral cultures,[26] limitations to interpretation of VL in serum and respiratory secretions exist. Ct may be low due to high viral RNA load without viable virus, no consistent Ct cutoff exists, and

variability in sample collection and reaction conditions may alter gene amplification.[10,27-29] Finally, time from initial SARS-CoV-2 infection was considered. The infectious period of SARS-CoV-2 peaks at symptom onset and declines over 10 d in immunocompetent patients and 15 d in immunosuppressed patients.[28] It is possible that the highly infectious period for our patient had passed at time of OLT, potentially reducing the chance of COVID-19 relapse during the postoperative period.

Although our patient exhibited active COVID-19 infection, it remained unclear what his outcome following OLT would be, but it was certain that without OLT, he would die. Waiting for 2 wks or a negative RT-PCR test was not feasible.[1] Patients can have prolonged detection of viral RNA without isolated active virus; this does not predict mortality nor inform about immune response.[12,28,30] Our patient exhibited prolonged RT-PCR positivity despite full antibody response. Allocation of a scarce organ resource in a patient with unknown outcome was also considered. Liver transplant centers across Canada were contacted as listing our patient as "high status" would result in our patient receiving the next available organ. All transplant centers were agreeable, and none reported encountering a similar case.

Before OLT, we considered treatment of COVID-19. We elected against using corticosteroids or tocilizumab, as benefits are only seen in patients requiring supplemental oxygen.[3] Our patient was intubated for airway protection, not hypoxemia. Yohanathan et al used remdesivir in their SARS-CoV-2 positive OLT recipient,[8] whereas we believed no evidence for its use in our patient existed, and it could cause transaminitis.[3,31] Convalescent plasma was not given due to lack of benefit in COVID-19, despite it being used by others.[3,7,8]

Immunosuppression may attenuate the immune response to COVID-19. Tacrolimus improves survival in LTR with COVID-19 without increasing the risk of severe COVID-19.[20,21] Conversely, mycophenolate mofetil (MMF) may increase the risk of severe COVID-19 in a dose-dependent manner.[21] Holding antimetabolite immunosuppressive agents have not been shown to increase risk of organ rejection.[32] With this evidence, we initiated tacrolimus immediately postoperatively, while MMF introduction was delayed to avoid initial over immunosuppression. A renal-sparing immunosuppression protocol was considered. Given that most patients with acute kidney injury in the setting of ALF have renal recovery after OLT,[33] along with the beneficial effect of tacrolimus in COVID-19, we proceeded with early tacrolimus initiation. Posttransplant biopsy confirmed this strategy of immunosuppression, similar to others,[8] to be effective.

This case highlights challenges in risk stratification of patients awaiting OLT who become SARS-CoV-2 positive. Lack of data on long-term effect of COVID-19 in transplant recipients and effect of immunosuppression makes the decision difficult. Although the ethical concerns of allocating a scarce organ resource to a patient with unknown postoperative outcome must be recognized, exceptions to current guidelines are justified under specific circumstances.

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