Recurrent hepatic artery thrombosis following living donor liver transplant as sequelae of SARS-CoV-2 infection: case report

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Abstract

Background: As the second wave of COVID-19 is gripping the globe, liver transplant centers are increasingly receiving patients with a recent recovery from SARS-CoV-2 infection. Despite full clinical recovery, unexpected, unusual and potentially life-threatening complications in these patients are increasingly being recognized, one such patient is discussed here. By far, this is the first ever reported case of a COVID-19 recovered recipient developing recurrent thrombotic complications, which led us to change our routine anticoagulation protocols.

Case presentation: We performed liver transplantation on a 51-year-old gentleman with decompensated liver disease 23-days after recovering from SARS-CoV-2 infection. At the time of surgery, he had no known sequelae of COVID-19. His routine preoperative work-up showed no underlying coagulation disorders. He underwent living related liver transplant (modified right lobe graft) during which, despite massive blood loss and a prolonged anhepatic phase, his thromboelastographic (TEG) parameters persistently revealed hypercoagulability. He received anti-coagulation according to our standard protocol which is based on aPTT ratio and INR. After a brief uneventful early post-operative period, he developed hepatic arterial thrombosis (HAT) on the 14th postoperative day, and again after 4 days, both of which required surgical intervention. He was eventually discharged with normal graft function but was soon readmitted with recurrent HAT and necrosis of anterior sector with cholangiolar abscesses, further leading to graft loss, necessitating re-transplantation, from which he could not recover due to a rejection resistant to all conventional measures.

Conclusions: There is emerging evidence that patients following SARS-CoV-2 infection tend to be hypercoagulable. We believe that this hyper coagulability might have played a significant role in the development of hepatic arterial thrombosis and eventual graft loss in this patient. This highlights the importance of revisiting anticoagulation protocols in liver transplant recipients recovered from COVID-19 and base them on TEG rather than routine parameters such as INR and aPTT, which are routinely deranged in such patients.

Background

As the rapid emergence of the second wave of COVID-19 pandemic shows no signs of slowing down (1), transplant clinicians all over the world are facing the scenarios of more and more SARS-CoV-2 recovered patients presenting for solid organ transplantation (2). COVID-19 is still not fully understood with new symptoms, organ system involvements, and new complications emerging each day. Liver transplant (LT) recipients are a special population with several factors deciding the graft related and the overall outcome. There is a certain degree of uncertainty regarding the safety of performing liver transplantation in a patient who has recovered from SARS-CoV-2 infection. It has become apparent that COVID-19 is a multisystem disease (3), the extent of involvement varies significantly from patient to patient. When faced with a patient recovered from SARS-CoV-2 infection presenting for LT, clinicians are faced with a host of dilemmas including the latency of the virus, extent of systemic involvement, optimal timing of

surgery and appropriate post-operative immunosuppression. Not just the theoretical possibility of a flare-up of infection with immunosuppression, a worry which has been proven wrong as per reports, there are several other variables at play which may affect the new liver graft. Even more important is the wide array of emerging, unknown, and unexpected complications these patients have in the perioperative period which may adversely affect the graft related outcome.

One of the most common causes of graft loss following a liver transplant is vascular complication; either an inflow or an outflow disturbance. Vascular complications reported in COVID-19 patients may affect the liver grafts as well (4). In this report we describe the case of a patient with decompensated ethanolic chronic liver disease who underwent a living related liver transplant after recovering from SARS-CoV-2 infection and succumbed to unexpected but potentially avoidable complications which led us to change our management guidelines in such patients. To the best of our knowledge, this is the first reported case of recurrent arterial thrombosis following a liver transplant in a recipient recovered from SARS-CoV-2 infection. Our experience and changes in the protocol that we made should be a good guide to other liver transplant surgeons to guide anticoagulation in their patients.

Case Presentation

A 51-year-old male patient was admitted under our care in November-2020 with a diagnosis of ethanol related chronic liver disease (CLD), decompensated with ascites and encephalopathy and was evaluated for living related LT. He did not have any coagulation disorder on routine preoperative workup. All liver transplant recipients at our center are screened for COVID-19 before surgery as per our standard protocol (5). A routine COVID-19 RT PCR sent as part of his evaluation came positive. Symptoms were mild in the form of fever and occasional cough. He was quarantined and was started on a 5-day course of azithromycin in addition to the supportive management, following which his symptoms subsided. A repeat COVID-19 RT PCR after 14-days turned out to be negative. After weighing the potential unknown risks following a recent SARS-CoV-2 infection and the deleterious effects of further decompensation of the liver disease, it was decided to postpone his transplantation for a period of 2-weeks.

Once he was readmitted for transplant, all the investigations were repeated which included the routine set of pre-transplant tests as well as interleukin-6, C-reactive protein, lactate dehydrogenase (LDH), and ferritin. The preoperative investigations have been summarized in **Table 1**. A high-resolution computed tomography (CT) of chest was done to rule out any sequelae of COVID-19 pneumonia, which revealed small patchy ground glass opacities in the right lower lobe with no interstitial thickening, a CT score of 8/25. The patient and his family members were thoroughly explained regarding the unknown risks of SARS-CoV-2 and the possible impact on graft related outcome. After obtaining adequate consent from the patient as well as required clearances from a multi-disciplinary clinical team, it was decided to go ahead with transplantation procedure 23-days after recovering from COVID-19 disease.

Conduct of anesthesia was done as per our standardized institutional protocol. The dissection phase was complicated by profuse surgical bleeding owing to dense adhesions. Packed red cells were transfused

aiming at a hemoglobin level of 9 gm/dl. Administration of platelets, plasma and cryoprecipitate was based on the thromboelastogram (TEG) which was repeated 2-hourly. The intraoperative TEG readings are given in **Table 2**. Due to significant bleeding from dense perihepatic collaterals, recipient hepatectomy was done with porta-first approach, prolonging the anhepatic time. Despite significant bleeding, and prolonged anhepatic time of 4-hours, it was noticed that the patient maintained a hypercoagulable TEG throughout the surgery, as evidenced by a coagulation index value of more than +3. A total of 20 packed red cell units and 8 units of fresh frozen plasma were transfused intraoperatively. He received the modified right lobe graft (right lobe without middle hepatic vein), and segment 5 and segment 8 veins were reconstructed using a PTFE graft to fashion a neo-middle hepatic vein. Graft implantation was uneventful with standard hepatic vein and portal vein anastomoses. Graft had a single artery which was anastomosed with recipient's right hepatic artery (which originated from common hepatic artery) using interrupted 8-0 prolene sutures. There was no tension, redundancy, or luminal discrepancy in arterial anastomosis. Recipient's left hepatic artery originated from left gastric artery (replaced left gastric artery-type 2 anatomy) and was ligated. The rest of the surgery was uneventful and the patient was shifted to the post-transplant intensive care unit for further management.

Inotropic support was weaned off and the patient was extubated on the 2nd post-operative day. Post-operative antibiotic therapy included cefoperazone-sulbactam, teicoplanin, metronidazole and fluconazole. Low dose immunosuppression was started on the evening of first post-operative day using tacrolimus and mycophenolate mofetil along with tapering doses of methylprednisolone which was later changed to oral prednisolone. Patient tolerated the incremental doses of immunosuppression well which was tailored according to the patients LFT's and tacrolimus trough levels. As per our standard anticoagulation protocol (discussed later), he did not receive heparin infusion during or in immediate postoperative period due to deranged prothrombin time – international normalized ratio (INR) and activated partial thromboplastin time (aPTT) ratio, both being more than 2, although all postoperative TEGs remained normal to hyper-coagulable.

Anticoagulation was started from 3rd post-operative day in the form of low molecular weight heparin and was discontinued on the 10th post-operative day when aspirin 75-mg once daily was initiated. Early post-operative course was satisfactory with near normalization of liver enzymes by the 7th day post transplantation. As per the protocol at our center, ultrasound doppler of liver graft were done twice daily for first five postoperative days and then once daily from sixth to tenth postoperative day; all doppler studies revealed normal inflows and outflows, homogenous graft and no intra-hepatic biliary dilatation.

While patient's liver function tests showed recovery as expected, a repeat doppler done on the 14th day of transplantation revealed absent hepatic arterial flow. A CT angiography of liver was done immediately which confirmed hepatic artery thrombosis (HAT). Digital subtraction angiography guided thrombolysis/thrombectomy was attempted but was unsuccessful. The patient was taken for emergency re-exploration. Intra-operatively, the graft was homogenous with no signs of ischemia. Graft artery had no visible or palpable pulsations. The arterial anastomosis was disassembled. A fleshy thrombus was

present in the recipient artery extending to the root of common hepatic artery. Thrombectomy of the right hepatic artery was done using a 2-Fr Fogarty catheter. Vascular patency was satisfactory after the procedure and he was shifted to the intensive care unit and started on low molecular weight heparin for anticoagulation. Immediately post-exploration, his liver enzymes increased, which started coming down the subsequent days. Unfortunately, he again developed HAT on the 18th day of transplantation (4 days after re-exploration). He was taken up for a re-exploration. Thrombectomy was done and an autologous saphenous vein graft was used as conduit to anastomose the graft hepatic artery with left gastric artery. In view of recurrent HAT, it was decided to initiate him on hyperbaric oxygen therapy. He received a total of 4 cycles of hyperbaric oxygen therapy which were uneventful. By the end of 27th day post-transplant, he had near normalization of LFTs, normal inflows and outflows of the graft and hence he was discharged on the 30th post-operative day continuing low molecular weight heparin and with advices for a strict follow-up.

On the 18th day post discharge, he presented to our hospital with complaints of fever and chills. Abdominal imaging revealed presence of a cholangiolar abscess (Figure 1) with absent hepatic artery flow yet again. He was admitted & initiated on broad spectrum antibiotics. The blood investigations revealed leukocytosis and transaminitis (**Table 1**). Initially, he was managed with percutaneous drainage of the major abscesses. However, with persistent transaminitis and graft abscess, the patient and his family were counselled regarding the loss of graft and need for a retransplant after control of sepsis, to which he consented. Identifying and evaluating a new donor took us 2 weeks during which we were able to control his infection. He was taken up for re-transplantation 70 days after the initial transplantation.

Surgery for re transplantation was eventful, requiring massive blood transfusion and inotropic support. Once in the ICU, we encountered great difficulty in weaning him off inotropes due to persistent vasoplegia as evidenced by the cardiac output monitor and echo cardiogram. His liver enzymes and bilirubin started increasing by the 3rd post-operative day following a brief period of 2 days where the enzymes seemed to touch baseline. As there were no signs of infection or any vascular & biliary complication, we decided to treat it as acute cellular rejection using steroid pulses and antithymocyte globulin after performing a liver biopsy.

His clinical condition failed to improve with further worsening of hemodynamics & Liver function tests. His liver biopsy revealed centrilobular necrosis with cholestasis and no evidence of inflammatory infiltrate. We rationalized the drugs and performed 2 cycles of plasmapheresis keeping in mind the possibility of acute cellular rejection along with drug induced liver injury. In spite of our best efforts his clinical condition deteriorated with development of multiorgan failure. He suffered an irreversible cardiac arrest 80 days after the initial surgery.

Discussion And Conclusions

COVID-19 recovered patients presenting for liver transplantation are going to be increasingly frequent in the coming years. There is limited evidence regarding the sequelae of SARS-CoV-2 and its impact on

perioperative recovery (3). The ASA-APSF joint statement on elective surgery and anesthesia for patients after COVID-19 infection suggested a waiting period of 4-weeks after recovery in case of asymptomatic or mildly symptomatic patients (6). Other major surgical and anesthesia associations have also given similar protocol (7). Even though, these guidelines were not available at the time of our case, we followed our institutional protocol to ensure a complete clinical and radiological recovery along with normal inflammatory markers such as IL-6, D-Dimer and ferritin at the time of transplant (5).

This was our first liver transplant in a COVID-19 recovered recipient. Hyper coagulability (4), reactivation of latent virus with immunosuppression and occult multi systemic sequelae of COVID-19 were our main concerns in this patient. Fortunately, despite intense immunosuppression, we did not find any clinical or molecular evidence of SARS-CoV-2 in the post-operative period. However, the first liver transplantation in this patient was complicated due to the recurrent HAT during the post-operative period, which ultimately led to a loss of the transplanted graft. Even though technical aspects might have contributed to the occurrence of HAT, we do believe that hyper coagulability did play a significant role. The standard anticoagulation protocol which we use for all post liver transplant patients and is in place for more than 6 years, is based on the regular monitoring of aPTT and maintaining a ratio of patient's aPTT-to-control value between 2-2.5. The same protocol was used for this patient. As this patient had a deranged aPTT and INR in immediate postoperative period, which is not unexpected in these patients, anticoagulation was not initiated during or immediately after surgery, though TEG showing a contradictory picture of hypercoagulability. This led to change in our protocol as discussed below.

There is a growing pool of data which suggests patients infected by SARS-CoV-2 virus tend to be hypercoagulable (8,9). Many reports have come with evidence of acute arterial thrombosis in patients infected with SARS-CoV-2. TEG is a better predictor of coagulation parameters than the conventional parameters, such as INR and aPTT (10). Thromboelastographic studies have demonstrated significant hypercoagulopathy in a majority of these patients (11). This was along the lines of our experience in this case where the patient demonstrated significant hyper coagulopathy in spite the presence of clinically significant bleeding. It is interesting to note that duration of hypercoagulability post COVID-19 infection isn't well known and based on our experience it may well persist to more than 4 weeks post – infection.

We now believe that the patient should have been started on novel anticoagulants after discontinuing heparin on the 10th post-operative day. Novel anti coagulants are well tolerated orally, have rapid onset and offset of action along with fewer drug interactions and predictable pharmacokinetics (12). Probably demonstration of hyper coagulability by a TEG pre-operatively would have helped in better management of anticoagulation in this case. Starting unfractionated heparin intraoperatively might be a good idea in such cases but wasn't done in our case as the patient had clinically significant bleeding.

Our patient developed acute cellular rejection post operatively after the re-transplantation. Dhand et al reported a similar experience with a COVID-19 recovered patient presenting for liver transplantation which was successfully managed by high dose of steroids and T-cell depletion (2). In our case we were unable to successfully manage the graft dysfunction in spite of early initiation of intense immunosuppression by

means of steroid pulses, anti-thymocyte globulin and plasmapheresis. The presence of cholestasis in the liver biopsy indicates the presence of drug induced liver injury (DILI) in addition to acute cellular rejection. This was probably the result of a prolonged course of antibiotics following development of cholangiolar abscesses which continued well into the post-operative course following second liver transplant as well.

Following our experience with this patient, we changed our anticoagulation protocols for COVID-19 recovered recipients to a TEG based protocol. We target to keep the coagulation index below +1 and act according to each of the parameters of TEG. The heparin infusion is started intraoperatively and is continued postoperatively based on TEG despite aPTT and PT-INR being deranged. Further, we have increased the duration of routine doppler surveillance of such recipients to 2 weeks at the end of which a CT angiography is done and doppler study is then continued alternate day for rest of the hospital stay. These patients are also started on oral anticoagulants at discharge which are continued atleast till 3-months.

We believe that our experience will throw some valuable insights about managing liver transplant in a patient recovered from SARS-CoV-2 infection. This was the first case of graft loss after nearly 400 cases in our institute in the last 4 years. Significant hyper coagulability probably had a significant impact in the development of hepatic arterial thrombosis in this patient and subsequent loss of graft. Keeping in mind the pandemic proportions and the ambiguity regarding the effects of SARS-CoV-2, thorough multi systemic evaluation should be performed even for asymptomatic COVID-19 recovered patients presenting for solid organ transplantation. Hypercoagulability and vascular thromboses should be considered as unexpected, yet preventable complication of SARS-CoV-2 infection in liver transplant recipients. Transplant centers may modify and adopt the anticoagulation protocol that we have adopted in this special population as these patients tend to have intrinsic hypercoagulability despite deranged coagulation markers such aPTT and PT-INR or a low platelet count. Furthermore, this hypercoagulability is best assessed by TEG, and it should be routinely used to guide anticoagulation in these patients.

Abbreviations

APSF	Anesthesia Patient Safety Foundation
aPTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
CLD	Chronic liver disease
CT	Computed tomography
HAT	Hepatic artery thrombosis
INR	International normalized ratio

LDH	Lactate dehydrogenase
LFT	Liver function test
LT	Liver transplant
RT PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TEG	Thromboelastogram

Declarations

Ethics approval and consent to participate: Ethical approval was not required and was waived.

Consent for publication: Informed-written consent was received from the primary family member who was legal representative of the patient for inclusion of patient's data in this case report.

Availability of data and materials: Not applicable.

Competing interests: Authors declare no conflict of interests.

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Author's contributions: All authors were directly involved in the management of this patient. N Goyal was the primary surgeon operating on the patient, while V Arunkumar and S Singhal assisted in the surgery. Perioperative management was done by A Raj, V Shankar, and HK Garg. Manuscript was written by A Raj, V Shankar, and S Singhal. N Goyal, V Arunkumar, and HK Garg helped with revision of manuscript. All authors approved the manuscript in its final form.

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References

1. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Apr 25]. Available from: <https://covid19.who.int>
2. Dhand A, Bodin R, Wolf DC, Schluger A, Nabors C, Nog R, et al. Successful liver transplantation in a patient recovered from COVID-19. *Transpl Infect Dis*. 2021 Apr;23(2):e13492.
3. Bui N, Coetzer M, Schenning KJ, O'Glasser AY. Preparing previously COVID-19-positive patients for elective surgery: a framework for preoperative evaluation. *Perioper Med (Lond)*. 2021 Jan 7;10(1):1.
4. Abou-Ismaïl MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res*. 2020 Oct;194:101–15.

5. Olson MT, Triantafyllou T, Singhal S. Optimal Diagnostic Strategy for Coronavirus Disease 2019 Detection in Liver Transplant Recipients: Critical Review of Available Evidence. *Apollo Medicine*. 2021;10.
6. ASA and APSF Joint Statement on Elective Surgery and Anesthesia for Patients after COVID-19 Infection [Internet]. [cited 2021 Apr 25]. Available from: <https://www.asahq.org/about-asa/newsroom/news-releases/2020/12/asa-and-apsf-joint-statement-on-elective-surgery-and-anesthesia-for-patients-after-covid-19-infection>
7. Olson MT, Triantafyllou T, Singhal S. Resumption of elective surgery during the COVID-19 pandemic: what lessons can we apply? *Eur Surg*. 2020 Jun 5;1–3.
8. Osilli D, Pavlovica J, Mane R, Ibrahim M, Bouhelal A, Jacob S. Case reports: mild COVID-19 infection and acute arterial thrombosis. *J Surg Case Rep*. 2020 Sep;2020(9):rjaa343.
9. Al Mahruqi G, Stephen E, Abdelhedy I, Al Wahaibi K. Our early experience with mesenteric ischemia in COVID-19 positive patients. *Ann Vasc Surg*. 2021 Jan 27;
10. Raj A, Shankar V, Singhal S, Dhar P, Krishnan L, Goyal N, et al. Thromboelastogram Demonstrates Significant Hypercoagulability in Patients Undergoing Right Donor Hepatectomy - A Prospective Single-Center Analysis. *International Journal of Transplantation Research and Medicine*. 2020 Apr 15;6.
11. Bocci MG, Maviglia R, Consalvo LM, Grieco DL, Montini L, Mercurio G, et al. Thromboelastography clot strength profiles and effect of systemic anticoagulation in COVID-19 acute respiratory distress syndrome: a prospective, observational study. *Eur Rev Med Pharmacol Sci*. 2020 Dec;24(23):12466–79.
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020 May;18(5):1094–9.

Tables

Table 1 : Blood investigations at the time of COVID-19 and before each transplant.

Investigations	On Admission for COVID-19	1-day before first transplant	1-day before retransplant
Hemoglobin (g/dl)	11.6	10.8	9.2
WBC count (/mm ³)	5400	4300	6400
Platelet (/mm ³)	132000	150000	180000
INR	1.9	2.1	1.9
Urea (mg/dl)	32	32	56
Creatinine (mg/dl)	0.8	1.0	0.9
Total Bilirubin (mg/dl)	2.3	2.1	1.9
AST (U/L)	65	59	65
ALT (U/L)	62	35	43
ALP (U/L)	54	53	145
Albumin (g/dl)	3.5	3.2	3.2
IL-6 (pg/ml)	32	15	
Ferritin (ng/ml)	300	100	
Procalcitonin (ng/ml)	<0.5	<0.5	0.6

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL-6, interleukin-6; INR, international normalized ratio; WBC, white blood cells.

Table 2: Intraoperative TEG values

	R (minutes)	K (minutes)	α (degrees)	MA (mm)	LY 30 (%)	CI
Dissection phase	3.9	2.1	72	76	1.2	6.32
Anhepatic phase	4.4	1.5	72	70	0.7	5.3
Neo-hepatic phase	3.6	1.2	80	73	1.1	5.5

α , alpha or the angle; CI, coagulation index; K, kinetic value; LY 30, lysis after 30 minutes; MA, maximum amplitude; R, reaction time; TEG, thromboelastogram.

Figures

Figure 1

(a) Arterial phase of CT angiography on 14th postoperative day of first liver transplant showing no intrahepatic arterial filling. (b) Developing abscess at the time of readmission. These abscesses were drained through percutaneous pigtail drain placement. (c) Abscess cavity with graft loss (majorly anterior sector) before second liver transplant.

Clinical course											
Days	-37	-23	-2	0	2	14	18	30	48	70	80
Clinical Events	Diagnosed COVID-19+	First RT PCR negative	Second RT PCR negative	First LDLT	Extubated	First HAT	Second HAT	Discharged	Admitted with HAT+ Abscess	Redo LDLT	Death

Figure 2

Graphical Timeline of the critical events. HAT, hepatic artery thrombosis; LDLT, living donor liver transplant; RT PCR, reverse transcriptase polymerase chain reaction.

Supplementary Files

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