Invasive Pulmonary Aspergillosis and Tuberculosis Complicated by Hemophagocytic Lymphohistiocytosis - Sequelae of COVID-19 in a Liver Transplant Recipient

Akash Gandotra [*], Rohit Mehtani [*], Madhumita Premkumar [*], Ajay Duseja [*], Arka De [*], Nabhajit Mallik [†], S. Durgadevi [†], Ashim Das [‡], Naveen Kalra [§]

[*]Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [†]Department of Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [‡]Department of Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India and [§]Department of Radiodiagnosis, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Liver transplant recipients are at an increased risk of opportunistic infections due to the use of immunosuppression. Coronavirus disease of 2019 (COVID-19) increases the risk of these infections further due to associated immune dysfunction and the use of high-dose steroids. We present a case of a liver transplant recipient who developed disseminated tuberculosis and invasive pulmonary aspergillosis complicated by acquired hemophagocytic lymphohistiocytosis after recovering from severe COVID-19. (J Clin Exp Hepatol 2022;12:1007–1011)

Liver transplant recipients are associated with adverse outcomes after infection with coronavirus disease of 2019 (COVID-19).[1] Use of high dose immunosuppression has also led to a rise in cases of invasive aspergillosis worldwide.[2] We describe a case highlighting the role of post-transplant immunosuppression and COVID-19 in causing reactivation of tuberculosis and invasive pulmonary aspergillosis, complicated by acquired Hemophagocytic Lymphohistiocytosis (HLH).

CASE REPORT

We report the case of a 47-year-old gentleman who underwent a living donor liver transplant in 2018 for chronic hepatitis B and hepatitis C co-infection related decompensated cirrhosis and hepatocellular carcinoma (HCC) within Milan criteria. Post-transplant, his liver functions were stable on maintenance immunosuppression with Sirolimus 2 mg twice a day. He had an early recurrence of HCC three months post-transplant, which was managed with a combination of lenvatinib and locoregional therapy in the form of two sessions of microwave ablation (MWA) and two sessions of doxorubicin drug-eluting bead transarterial chemoembolization (DEB-TACE) and was in remission since the last 18 months as determined by serial imaging as per mRECIST (modified response evaluation criteria in solid tumors) criteria. The patient developed new-onset diabetes after transplant (NODAT) a year ago and was on metformin therapy. The patient tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the month of March 2021 after complaining of two weeks of fever and dry cough.

He had not been vaccinated for coronavirus disease of 2019 (COVID-19) at the time of infection. He was found to have moderate COVID-19 due to the presence of respiratory distress, for which he required admission in outside hospital for 3 days where his immunosuppression was switched from sirolimus (4 mg per day) to oral prednisolone (40 mg per day for a week, followed by 10 mg daily). He also received low molecular heparin for 7 days. Ten days later, he complained of progressive shortness of breath along with high-grade fever and fatigue. At this admission, he tested negative for COVID-19 on the SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) report. On examination, he had tachycardia, tachypnea, and hypoxemia, with chest crepitations, and a palpable spleen. He required high

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Address for correspondence: Dr. Madhumita Premkumar Associate Professor, Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, 160012, India. Tel.: +91 7087003409.
E-mail: drmadhumitap@gmail.com
Abbreviations: AFB: Acid-fast bacilli; AKI: Acute kidney Injury; ATT: Antitubercular therapy; BDG: Beta-D Glucan; COVID-19: Coronavirus disease of 2019; DEB-TACE: Drug eluting bead transarterial chemoembolization; GM: Galactomannan; HCC: Hepatocellular Carcinoma; HLH: Hemophagocytic Lymphohistiocytosis; HRCT: High-resolution computed tomography; IDSA: Infectious Diseases Society of America; IPA: Invasive pulmonary aspergillosis; IVIg: Intravenous immunoglobulin; mRECIST: modified response evaluation criteria in solid tumors; NODAT: New onset diabetes after transplant; PAS: Periodic acid Schiff; RT-PCR: Reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome corona virus 2; sHLH: Secondary hemophagocytic lymphohistiocytosis
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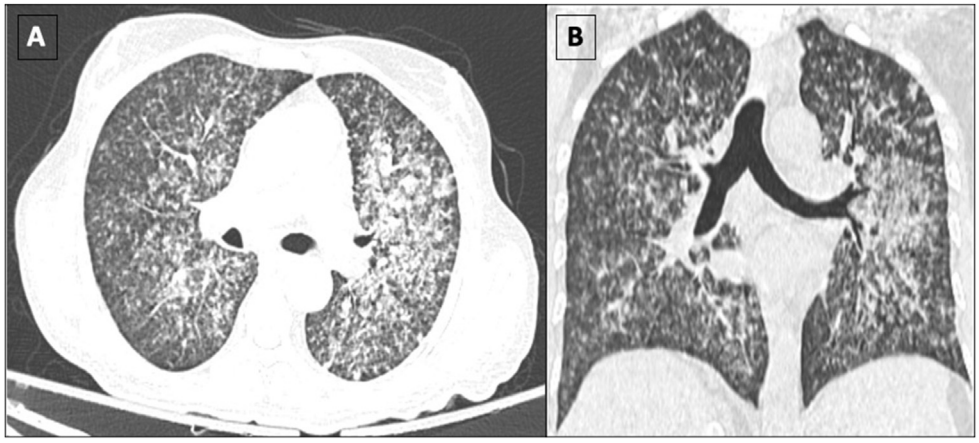

Figure 1 Axial (A) and Coronal (B) reformatted sections in lung window settings showing multiple centrilobular and coalescing acinar nodules in both lungs, predominantly in the left upper and middle lobe. Features are consistent with infective aetiology.

flow oxygen by Venturi-mask with an FiO_2 of 60%. Laboratory investigations were suggestive of pancytopenia, acute kidney injury (AKI), elevated liver enzymes, and elevated serum procalcitonin (Table 1). Ultrasound of the abdomen revealed splenomegaly with a spleen size of 17 cm. A high-resolution computed tomography (HRCT) scan of the chest revealed bilateral multiple diffuse centrilobular and acinar coalescing nodular opacities suggestive of an infective etiology (Figure 1). In view of fever, pancytopenia, splenomegaly, and calculated H-score being 306 (Table 2), secondary hemophagocytic lymphocytic histiocytosis (HLH) was suspected. He had serum ferritin of 27717 μg/L and fibrinogen levels of 0.8 mg/dL. Bone marrow examination revealed increased histiocytes, with many showing hemophagocytosis (Figure 2A and 2B), thus confirming the diagnosis of secondary HLH. Bone marrow biopsy additionally showed multiple necrotizing granulomas (Figure 2C); however, stains for acid-fast bacilli (AFB) and periodic acid-Schiff (PAS) did not reveal any organisms. Sputum microscopy was positive for acid-fast bacilli on Ziehl–Neelson stain, and sputum fungal culture grew *Aspergillus flavus*.

He was managed with intravenous immune globulin for HLH, liposomal Amphotericin B, and antitubercular therapy (ATT). In view of elevated procalcitonin, AKI, and multiorgan involvement, he received intensive fluid management along with broad-spectrum antibiotic coverage with intravenous meropenem. Liposomal amphotericin B was switched to oral Posaconazole after 3 weeks. AKI was likely prerenal as there was no proteinuria, and it improved with fluid resuscitation. He improved clinically with the resolution of fever, hypoxia, and pancytopenia. He was switched again to sirolimus-based immunosuppression, with complete resolution of cytopenia after 7 days of therapy (Table 1). A repeat positron emission tomographic scan revealed resolution of chest nodules and old neoplastic lesions with post TACE/ablation changes in the graft liver. The patient has completely recovered and is on modified antitubercular therapy and tapering steroid/sirolimus immunosuppression.

DISCUSSION

Infectious complications remain important preventable causes of morbidity and mortality among liver transplant patients. Opportunistic infections, including mycobacterium tuberculosis infection and invasive fungal infections, occur most commonly 1–6 months post-transplant when

Table 1 Laboratory Parameters of the Patient.

Parameters	At Admission	On Follow-up
Hemoglobin (g/dL)	8.1	10.1
Total Leukocyte Count (per cu. mm.)	1600	9700
Platelet count ($\times 10^3$ per cu. mm)	11	362
Serum Sodium (mEq/L)	128	136
Serum Potassium (mEq/L)	5.38	3.8
Blood Urea (mg/dL)	133	97
Serum Creatinine (mg/dL)	2.39	1.09
Serum Bilirubin (mg/dL)	1.87	1.6
Aspartate Aminotransferase (Units/L)	404	98
Alanine Aminotransferase (Units/L)	195	36
Alkaline Phosphatase (Units/L)	636	720
Prothrombin Index (PTI; %)	63	92
International Normalized Ratio (INR)	1.55	1.02
Serum Ferritin (μg/L)	27717	245
Lactate Dehydrogenase (Units/L)	457	231
Procalcitonin (ng/mL)	20	0.34
Fibrinogen (mg/dL)	0.8	2.6
Triglycerides (mg/dL)	417	132

Table 2 H-score Criteria (2014) for Diagnosis of HLH and H-score of the Index Patient.

Parameters	Number of points (criteria for scoring)	Index case
Known underlying immunosuppression	No (0), yes (18)	18
Temperature (°C)	<38.4 (0), 38.4–39.4 (33), >39.4 (49)	33
Organomegaly	No (0), hepatomegaly or splenomegaly (23), hepatomegaly and splenomegaly (38)	23
No. of cytopenias	1 lineage (0), 2 lineages (24), 3 lineages (34)	34
Ferritin (ng/ml)	>2000 (0), 2000–6000 (35), >6000 (50)	50
Triglyceride (mg/dl)	>132.7 (0), 132.7–354 (44), >354 (64)	64
Fibrinogen (g/l)	>2.5 (0), ≤2.5 (30)	30
AST (U/L)	<30 (0), ≥30 (19)	19
Hemophagocytosis features on bone marrow aspirate	No (0), yes (35)	35
Total H-score		306
Probability of sHLH		>99%

immunosuppression is at its peak.[3] A systematic review showed that liver transplant recipients have an 18-fold increased risk of active tuberculosis infection than the general population and four times increased mortality.[4] A systematic review and meta-analysis demonstrated dyspnoea on presentation, hypertension, diabetes mellitus, use of corticosteroids and age 60 years or older to be significantly associated with increased mortality.[5] Initially liver transplant recipients were considered to be at increased risk of adverse outcomes due to COVID-19, however, a recent systematic review and meta-analysis demonstrated similar outcomes in liver transplant recipients as nontransplant recipients.[6]

This case shows the tricky management of post-COVID-19 sequelae in a liver transplant recipient who was on immunosuppression, multikinase inhibitor therapy, with background diabetes and HCC in remission. In the index case, sirolimus was switched to prednisolone at the time of diagnosis of COVID-19. Theoretically, Sirolimus is expected to reduce infection in high-risk populations and severity of COVID-19;[7] however, the evidence for the same is lacking. The proven benefit of steroids in improving mortality in patients with severe COVID-19[8] could have led to the decision to switch to prednisolone for immunosuppression in the index case. However, the use of steroids for COVID pneumonia resulted in reactivation of tuberculosis, superadded invasive pulmonary aspergillosis, and granulomatous inflammation in the marrow leading to secondary HLH. Diagnosis of tuberculosis was based on the presence of acid-fast bacilli in the sputum; however, culture for mycobacteria tuberculosis or molecular assays was not done. Although alkaline phosphatase

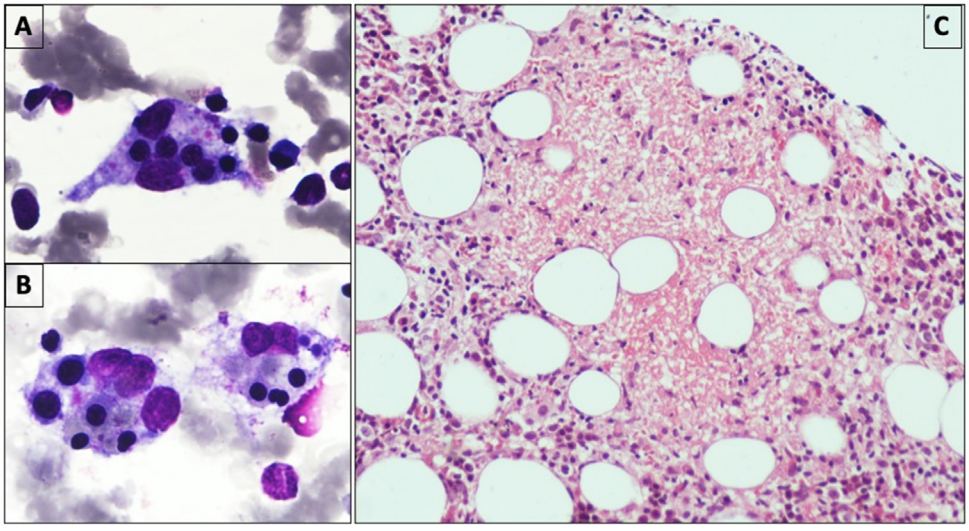

Figure 2 Bone marrow aspirate showing many histiocytes with ingested erythroid precursors and platelets (A & B: May-Grunwald-Giemsa, × 1000). Bone marrow biopsy showing necrotizing granulomatous inflammation (C: Hematoxylin & Eosin, × 200).

was markedly raised in the index case, a liver biopsy to demonstrate granulomatous involvement of the liver was not performed as the patient was started treatment for both disseminated TB and HLH, and no additional information was expected from a liver biopsy. A diagnosis of probable invasive pulmonary aspergillosis (IPA) was as per the Infectious Diseases Society of America (IDSA) guidelines with CT imaging, aspergillus culture positivity in a sputum sample, and raised BDG/GM as biomarkers.[9] Broncho-alveolar lavage or lung biopsy was not done due to the poor general condition of the patient.

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a life-threatening syndrome of excessive immune activation that results in a hyperinflammatory state and consequently tissue destruction. Acquired HLH after COVID-19 infection is seen in about 6.3% of cases and is associated with a high mortality.[10] A majority of HLH cases occur during the active phase of the disease; however, recent reports have highlighted the development of HLH even after the patient has recovered from COVID-19,[11,12] as was seen in our index case. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.[13] Treatment options include steroids, immunoglobulins, and interleukin inhibitors.[14] High suspicion is needed to diagnose sHLH. Our patient was successfully managed by timely intravenous immunoglobulin (IVIg) with biopsy confirming the presence of both hemophagocytosis and granulomatous inflammation.

Disseminated tuberculosis was the third infection picked up during this admission. Many cases of reactivation of disease have been reported in the light of the COVID-19 pandemic.[15,16] Worsening of glycemic control after reintroduction of steroids and COVID-19-related immune dysfunction could have all contributed to this presentation.

Management of late post-transplant infections remains a challenge in the COVID-19 era. Our unique case indicates the timely detection and treatment of IPA and disseminated tuberculosis post-COVID-19 infection, complicated by sHLH, in a liver transplant patient with a successful outcome.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Akash Gandotra – Writing – original draft; ***Rohit Mehtani*** – Writing – review & editing; ***Madhumita Premkumar*** – Conceptualization, writing – review and editing, data curation; ***Ajay Duseja*** – Writing – review and editing; ***Arka De*** – Writing – review and editing; ***Nabhajit Mallik*** – Investigation, Writing – review and editing; ***Durgadevi S*** - Investigation, Writing – review and editing; ***Ashim Das*** - Investigation, Writing – review and editing; ***Naveen Kalra*** – Investigation, Writing – review and editing.

CONFLICTS OF INTEREST

The authors have none to declare.

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ARTICLE GUARANTOR

The first author, Dr Akash Gandotra, is a Fellow in the Department of Hepatology, PGIMER, Chandigarh. The attending physician, Dr. Madhumita Premkumar is the article guarantor.

CONSENT

Informed consent was obtained from the patient regarding publishing this case report.

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