

Recovery of moderate COVID-19 disease in a liver transplant recipient on continued immunosuppression

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Case Report

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Abstract

Background

The global outbreak of severe acute respiratory syndrome coronavirus 2 has had an enormous impact on the world. It remains unclear to what extent liver transplant recipients should be considered at a higher risk of severe disease due to the limited data available.

Case presentation

We describe a moderate course of COVID-19 in a patient who underwent a liver transplant two years earlier due to Budd-Chiari syndrome. She presented with malaise, headache, dry cough and fever for four days. Immunosuppressive therapy with tacrolimus and mycophenolate mofetil was continued throughout the course of infection, oxygen therapy was given for a single night and the patient gradually recovered with supportive care only.

Conclusions

With this case report, we demonstrate that liver transplantation and immunosuppression is not necessarily associated with severe COVID-19 disease and emphasize that more information on this matter is urgently required. Withdrawal of immunosuppressive therapy could be associated with a higher mortality.

Background

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus disease 2019 (COVID-19), has had an enormous impact on the world. Since the beginning of the outbreak, researchers worldwide have tirelessly tried to understand the disease. However, at this point, it remains unclear to what extent liver transplant recipients should be considered at a higher risk of severe disease due to the limited availability of studies. Consequently, we describe and discuss a case of moderate COVID-19 in a liver transplant recipient in continued immunosuppressive therapy.

Case Presentation

A 58-year-old female, who had a liver transplantation two years earlier due to Budd-Chiari syndrome, was admitted to the Department of Hepatology and Gastroenterology with malaise, headache, dry cough and fever for four days. She denied other complaints. There was no recent travel history or any known exposures to SARS-CoV2. She had a medical history of hypertension, hypercholesterolemia, obesity (BMI 37.1 kg/m²) and had been treated for cholangitis shortly after her liver transplantation. The patient had no alcohol abuse and was a previous smoker but stopped before transplantation. At admittance, she had been on stable immunosuppression with tacrolimus 4 mg QD and mycophenolate mofetil 500 mg BID for

more than one year. Antihypertensive therapy consisted of amlodipine 5 mg and bendroflumethiazide with potassium 2.5+573 mg once daily.

On admission, the patient had a temperature of 38.6 °C, the blood pressure was 129/88 mm Hg, the heart rate 90 beats per minute, the respiratory rate 12 breaths per minute and the oxygen saturation 96% on ambient air. Her physical examination was inconspicuous and subsequent biochemistry with only modest signs of COVID-19 disease with C-reactive protein 9.8 mg/L (reference range < 8), creatinine 97 µmol/L (reference range, 45–90) and alkaline phosphatase 120 U/L (reference range, 35–105). Leukocytes were within normal ranges (reference range, 3.5–10.0). White blood cell differential was not conducted initially. Liver parameters were normal, and plasma-tacrolimus was within therapeutic range (5.1 µg/L).

A supine chest radiograph was without evident infiltrates. Urinary dipstick was normal. An oropharyngeal swab tested positive for SARS-CoV2 RNA using reverse-transcriptase-polymerase-chain-reaction (PCR) and nasopharyngeal swab was negative for influenza. Blood cultures were negative.

Due to penicillin allergy, she was treated intravenously with meropenem 1000 milligram TID for two days. On day 6 after onset of symptoms, the patient was clinically stable and discharged to self-isolation with continued immunosuppressive therapy without further treatment. She denied cardiopulmonary symptoms but complained of headache.

On day 11 after onset of symptoms, the patient was readmitted to the Department of Infectious Diseases complaining of increasing fever, fatigue, headache, and dyspnoea while walking on stairs. The body temperature was 38.6 °C and the oxygen saturation on ambient air 92%. Vital parameters were stable. During the first night, meropenem was reinitiated and she was given 1 litre of nasal oxygen per minute resulting in a saturation increase to 97%.

C-reactive protein was 5.1 mg/L, leukocytes 5.1×10^9 /L and lymphocytes 1.41×10^9 /L. Over the following three days, biochemistry was only modestly affected, with a maximum C-reactive protein of 37.2 mg/L, mild lymphopenia (1.11×10^9 /L, reference range 1.30–3.50), erythrocyte sedimentation rate 48 mm (reference range, < 30), albumin 32 g/L (reference range, 36–45), alkaline phosphatase 107 U/L, D-dimer 1.0 mg/l FEU (reference range, <0.60), and normal liver parameters.

Chest radiograph was still without infiltrates. Sputum was culture negative and PCR negative for *Mycoplasma pneumoniae* and *Legionella pneumophila* DNA.

After three days (day 14 after onset of symptoms), the patient improved, immunosuppressive therapy was again continued, while meropenem was discontinued and the patient was sent home to self-isolation.

Fifty days after onset of symptoms, the patient expressed a high degree of symptomatic improvement although fatigue and dyspnoea when walking outdoors and doing physical activities was still present.

Hypogeusia and anosmia had resolved spontaneously two weeks after discharge.

Discussion And Conclusions

We describe a case of moderate COVID-19 disease in a liver transplant recipient who recovered during continued immunosuppressive therapy. Additionally, this case shows that SARS-CoV2 infection in liver transplant recipients may present with a biphasic disease pattern as commonly described in COVID-19 and with clinical features similar to non-immunosuppressed individuals (1,2). Yet, in a recent report of kidney transplant-recipients with COVID-19 in New York City, fever appeared to be less common (3).

While the literature on COVID-19 is rapidly accumulating, it remains unclear whether liver transplant recipients are at higher risk of severe COVID-19 compared with non-transplant patients and the background population. Limited data suggests that COVID-19 may lead to more severe disease outcomes in liver and other solid organ transplant recipients with overall mortality rates up to 18% (3-5). However, pre-existing medical conditions associated with severe COVID-19 such as hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, obesity among others (2), may be more prevalent in liver transplant recipients (6), potentially increasing the risk of severe COVID-19 and blurring the impact assessment of immunosuppressive treatment in on COVID-19 disease. A recent nationwide study from Denmark, still in peer-review, found organ transplantation to be a significant but minor predictor for hospitalization and fatal outcome in SARS-CoV-2 PCR positive patients although only adjusting for sex and age (7).

While elevated alanine aminotransferase levels, reduced platelet counts and levels of albumin has been associated with an increased mortality (2), it has not yet been clarified whether these findings reflect underlying liver disease, direct liver damage or immune-mediated cell-injury. Nonetheless, abnormal liver parameters seem to be frequent in COVID-19 patients (8).

Despite the presence of co-morbidity such as obesity and hypertension in our case, which is normally associated with worse outcome in COVID-19 disease, one could speculate whether her current immunosuppressive treatment actually protected her from the severe outcome. In line with those considerations, it is currently being vividly discussed whether immunosuppression may induce protection from the viral induced hyperinflammatory syndrome characterized by cytokine storms and multi-organ failure or whether chronic immunosuppression constitutes a risk factor for severe disease (3,9). It has been suggested that all patients with severe COVID-19 should be screened for hyperinflammatory biomarkers to identify subgroups of patients for whom specific immunosuppression could improve outcome (9). For our patient, the course of disease was moderate and elaborated biomarker analysis was not conducted although that might be useful to potentially predict severe outcome (10). Preliminary data from Lombardy, Italy did not indicate an increased risk of severe COVID-19 in liver transplants in immunosuppression and reported a low mortality rate of 3% in long-term liver transplant recipients (11). In our case story, the patient was continued in immunosuppressive therapy without any adjustments. On the contrary, among the first case stories of SARS-CoV2 infected liver transplant recipients published,

temporary withdrawal of tacrolimus and administration of methylprednisolone 40 mg/day in a patient with severe lymphopenia was the presented (12). We speculate that increased mortality rates seen among organ transplant recipients could be associated with a reduction of immunosuppressive therapy (3).

A position paper from EASL-ESCMID has recently advised against reduction of immunosuppressive therapy and suggested that reduction should be considered only under certain circumstances (13) while other societies seems more prone to reduction (14). More studies are urgently needed to determine the implications of immunosuppressive therapy on COVID–19 disease. So, for now, adjustments in immunosuppressive therapy should be carefully individualized and factors such as COVID–19 disease severity, degree of lymphopenia, type of immunosuppressive regimen, time from transplantation and risk of acute graft rejection should be considered.

In conclusion, more evidence on COVID–19 in liver transplant patients is urgently needed to guide clinical management as these patients represent a potentially vulnerable cohort of patients. We suggest studies are conducted rapidly to determine the significance of immunosuppressive therapy.

Abbreviations

SARS-CoV2: severe acute respiratory syndrome coronavirus 2

COVID–19: Coronavirus disease 2019

BMI: Body Mass Index

QD: Quaque die (one per day)

BID: Bis in die (twice a day)

RNA: Ribonucleic acid

PCR: Polymerase chain reaction

TID: Ter in die (three times a day)

DNA: Deoxyribonucleic acid

EASL-ESCMID: The European Association for the Study of the Liver and the European Society of Clinical Microbiology and Infectious Diseases

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

VDM wrote first draft and did the literature research. The conception and design of the case report was conducted by VDM, SK og SL. All authors critically revised the article for important intellectual content. All authors approve of the final version of the article.

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References

1. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series [published online ahead of print, 2020 Mar 27] [published correction appears in *Lancet Infect Dis*. 2020 May 19;:]. *Lancet Infect Dis*. 2020;S1473-3099(20)30200-0. doi:10.1016/S1473-3099(20)30200-0
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. 2020 Mar 28;395(10229):1038] [published correction appears in *Lancet*. 2020 Mar 28;395(10229):1038]. *Lancet*. 2020;395(10229):1054- doi:10.1016/S0140-6736(20)30566-3

3. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation [published online ahead of print, 2020 Apr 24]. *N Engl J Med*. 2020;NEJMc2011117. doi:10.1056/NEJMc2011117
4. Lee BT, Perumalswami PV, Im GY, Florman S, Schiano TD. COVID-19 in Liver Transplant Recipients: An Initial Experience from the U.S. Epicenter [published online ahead of print, 2020 May 19]. *Gastroenterology*. 2020;S0016-5085(20)34703-X. doi:10.1053/j.gastro.2020.05.050
5. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter [published online ahead of print, 2020 Apr 24]. *Am J Transplant*. 2020;10.1111/ajt.15941. doi:10.1111/ajt.15941
6. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open*. 2015;5(5):e006971. Published 2015 May 14. doi:10.1136/bmjopen-2014-006971
7. Reilev M, Kristensen KB, Pottegaard A, et al. Characteristics and predictors of hospitalization and death in the first 9,519 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: A nationwide cohort. *medRxiv*05.24.20111823; doi: 10.1101/2020.05.24.20111823 (Preprint)
8. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests [published online ahead of print, 2020 Apr 13]. *J Hepatol*. 2020;S0168-8278(20)30218-X. doi:10.1016/j.jhep.2020.04.006
9. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0
10. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; 130: 2620–9.
11. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 2020;5(6):532- doi:10.1016/S2468-1253(20)30116-3
12. Liu B, Wang Y, Zhao Y, Shi H, Zeng F, Chen Z. Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient [published online ahead of print, 2020 Apr 3]. *Am J Transplant*. 2020;10.1111/ajt.15901. doi:10.1111/ajt.15901
13. Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep*. 2020;2(3):100113. doi:10.1016/j.jhepr.2020.100113.
14. APASL Covid-19 Task Force, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations [published online ahead of print, 2020 May 23]. *Hepatol Int*. 2020;1- doi:10.1007/s12072-020-10054-w