

Paris 22 Mai 2020

Dr. Alessandra Mazzola

Dear Professors Subrata Ghosh and Andrzej S Tarnawski

Editor-in-chief, Word Journal of Gastroenterology

Please find enclosed our Manuscript number 56538 entitled " **Case report of COVID-19 in a liver transplant recipient: Could iatrogenic immunosuppression have prevented severe pneumonia?**" which we hereby resubmit for revision, after taking into consideration the suggestions of the reviewers.

We were pleased to receive your letter and the constructive comments from your reviewers who have showed their interest in our case, and have clearly helped us to improve the paper. We have addressed all their comments and made all the modifications required in the revised version herewith. Our point-by-point responses to these comments, and the details of these changes, are listed below.

We look forward hearing from you, in the hope that your response will now be positive with respect to publication.

Sincerely yours,

Dr Alessandra Mazzola

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POINT BY POINT RESPONSES TO THE REVIEWER:

REVIEWER 1 REPORT:

I note same type error "Juliet 2019" "eventful despite". I suggest to the authors to make the effort to do a professional Editing to the manuscript.

We would like to thank the reviewer for his comments.

"Juliet 2019" was changed to "July 2019" (line 9 page 4, line 11 page 6).

"Eventful despite" was changed to "uneventful though there was no" (line 12 page 4).

REVIEWER 2 REPORT:

Minor revision:

1. Abstract-Case Summary: LT (LT) should be Liver Transplantation (LT).

We thank you the reviewer for his correction, "LT (LT) " was changed to "Liver Transplantation (LT)" (line 8 page 4).

2. Abstract-Case Summary and CASE REPORT-History of past illness: Juliet 2019 should be July 2019.

We completely agree with the comment, "Juliet 2019" was changed to "July 2019" (line 9 page 4, line 11 page 6).

3. CASE REPORT -Imaging examinations: Although the author states that this time the CT scan of the abdomen is of poor quality. However, I think it is necessary to describe the image in words. If there can be a comparison of previous checks, it might be better.

We agree with the comment; the figure of CT scan was modified to a clear picture (300 dpi) and more detail description have been added as reported:

"Figure 1: Chest computed tomography of a 58-year-old man who underwent liver transplantation in 2018. (A-C) Normal chest computed tomography of the patient in November 2019. (D-E) Chest computed tomography on admission in March 2020 showing ground-glass opacities with a peripheral distribution" (lines 1-4, page 21).

4. DISCUSSION: The content of this part makes the reader feel that it describes two different patients, one is infected with COVID-19 and one with SOT. I think it is necessary to compare SOT-COVID-19 patients with SOT patients alone, from the aspects of medical management, treatment, and prognosis follow-up. The discussion section should be revised.

We thank the reviewer for the interesting suggestion. We tried to propose a comparison between SOT-COVID patients and SOT patients alone in terms of the aspects of medical management, treatment, and prognosis follow-up..

In the text, we add in section **Discussion** the sentence:

“Also, few cases are recently reported in Lombardia transplant centre, in a Spanish series of SOT and in a Chinese report for a total number of 7 patients.^{7,8,9} The clinical characteristics and outcomes of COVID-19 LT patients are summarized in Table 2 (lines 13-15, page 9).

In the text, we add in section **Discussion-Symptoms** the sentences:

“Infections might be considered in the differential diagnosis in the case of changes in clinical status of SOT even in the absence of common signs or symptoms of infection. Data showed that, fever and physical signs of all types of infection in SOT patients, especially pulmonary and gastrointestinal infections, are diminished with subtle laboratory or radiological signs.¹⁰” (lines 2-4-, page 10).

“Also, in the Spanish case series, the authors reported 6 cases in liver transplant recipients: 5 of them presented with respiratory symptoms, one presented with only diarrhoea.⁸” (lines 8-9, page 10).

In the text, we add in the section **Discussion-Immunosuppression Management** the sentences:

“The risk of serious infections in SOT is determined by interactions between the patient’s epidemiological exposures and the state of immune suppression. In case of infection, the reduction in immunosuppression may be a useful component of antimicrobial therapy but with an increased risk of graft rejection or immune reconstitution syndromes. Reduction in specific immunosuppressive regimen should be roughly linked to the host responses desired for the pathogens encountered (e.g. steroids for bacteria and fungi, calcineurin inhibitors for viruses, cell cycle agents in neutropenia) recognizing that each agent has multiple effects on the immune system.¹⁰” (lines 6-10, page 11)

“In comparison with Lombardia experience, and in line with Spanish experience, no change in immunosuppression therapy was done^{7,8}. Although our patient neither stopped nor reduced immunosuppression, they had a favourable outcome using an experimental treatment” (lines 4-6, page 12).

In the text, we add in the section **Discussion-Treatment of COVID-19 Pneumonia and outcomes** the sentences:

“When infections occurs in SOT were associated with an increased risk of morbidity and mortality especially in the first three months after transplantation¹⁰. A rapid diagnosis and the beginning of a specific therapy consent an improvement in a clinical outcome” (lines 3-4, page 13).

“Moreover, few data are available regarding the outcomes on COVID-19 liver transplant patients. As reported in Table 2, three of among 111 patients liver transplant survivors (transplanted more than 10

years ago) died following severe COVID-19 disease⁷, 3 patients died in a Spanish series and , a fatal case of COVID pneumonia after 3 years of LT in a 59 old man with probably overlap chronic rejection was reported by Huang et al.⁹“(lines 16-17, page 13, line 1 page 14).

We added the Reference number 10: “J. A. Fishman. Infection in Organ Transplantation. Am J Transplant. 2017 Apr;17(4):856-879. Epub 2017 Mar 10 [PMID: 28117944 DOI: 10.1111/ajt.14208]” (lines 4-5, page 16).

5. Figure 1 is not clear. Need to change a clear picture, it is best to have more than 300dpi. It is best to have arrows to represent and describe.

The Figure was changed to a clear picture (300 dpi). (page 21)

SCIENCE EDITOR:

Issues raised:

1.I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

We thank you for your comments. We prepared and arranged the figure.

2. I found the “Case Presentation” did not meet our requirements. Please re-write the “Case Presentation” section, and add “FINAL DIAGNOSIS”, “TREATMENT”, and “OUTCOME AND FOLLOW-UP” section to the main text, according to the Guidelines and Requirements for Manuscript Revision.

We thank you for your corrections.

We have replaced the sentence CASE REPORT with “Case Presentation” (line 1 page 6).

We added the “FINAL DIAGNOSIS” as reported: “The radiological and virological aspects were strongly suggestive for COVID-19 pneumonia with gastrointestinal involvement in a LT patient.” (line 15-16, page 8)

We modified the “TREATMENT”: “No antibiotic treatment was administered” (line 2, page 9)

We added, in the “OUTCOME AND FOLLOW-UP” section the sentence: “After two months of COVID infection, no abnormalities have been found in terms of clinical examination and laboratory test during our medical consultation.“”(lines 7-8, page 9)

The “Case Presentation” section main text was modified according to the Guidelines and Requirements for Manuscript Revision.

3. The authors need to provide original informed consent signed by patients, and to fill out the CARE checklist form with page numbers.

We provided original informed consent signed by patients, and filled out the CARE checklist form with page numbers according to the Guidelines and Requirements for Manuscript Revision.