

April 17th, 2023

**Dr. Lian-Sheng Ma,  
World Journal of Gastroenterology.**

**Dear Dr. Ma,**

**Re: 84445-** Pulmonary hypertension, nephrotic syndrome, and polymyositis due to hepatitis C virus infection: a case report and literature review

Thank you for considering our paper and encouraging a revision. After reviewing reviewers' comments, we have improved the content in accordance with the reviewers' comments and have revised our manuscript accordingly. We confirm that all of the authors have approved the changes to the revised manuscript. We would be grateful if the revised manuscript could be further considered for publication in *World journal of Gastroenterology*, and we look forward to hearing from you soon.

Yours sincerely,

Ming Yu, MD, PhD,  
China-Japan Union Hospital of Jilin University,  
Email: yuming2019@jlu.edu.cn.

## **Response to technical Comments:**

### ***Editor Comments:***

#### ***(1) Science editor:***

The manuscript has been peer-reviewed, and it's ready for the first decision.

#### ***(2) Company editor-in-chief:***

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

Please visit our RCA database for more information at:  
<https://www.referencecitationanalysis.com/>.

**Res:** Thank you for helping us with our manuscript 84445. We have optimized figures in a single PowerPoint, and organized Tables in a single Word.

## **Response to Reviewer 1**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** the association between hepatitis C and autoimmune manifestations has been described for a long time, but case reports are important when faced with new combinations. The reports help us to be aware of such problems.

**Res:** We are grateful for the reviewer's affirmation.

## **Response to Reviewer 2**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The authors describe an unusual association of hepatitis virus C infection with three extrahepatic disorders as nephrotic syndrome, pulmonary infection and polymyositis. The manuscript is well written and interesting because such association has never been described. Virus C is often associated with extrahepatic disorders, but in the reported patient three different disorders were reported. Therapy with association of antiviral treatment and steroids resolved the complications of the disorders and the virus C negativization in a short time. Even if the association of a renal biopsy and a description of the behaviour of complement is lacking, the manuscript worth to be published due to the really unusual association of the pathologies and the rapid recovery.

**Res:** I want to thank the reviewer for the valuable comments. We will make further comprehensive revisions to the manuscript, once the manuscript is completed, we will follow the journal's recommended retouching agency to retouch the article.

### **Response to Reviewer 3**

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** This is a nice case report describing a patient diagnosed with pulmonary hypertension, nephrotic syndrome, and polymyositis due to chronic hepatitis C infection. A multi-disciplinary recommendation was that the patient should be treated with sildenafil and macitentan in combination and methylprednisolone. During treatment autoimmune symptoms, liver function, hepatitis C RNA levels, and cardiac parameters of right heart catheterization were monitored closely. The patient showed significant improvement in 6-minute walking distance from 100 to 300 m at 3-month follow-up and pulmonary artery pressure drops to 50 mmHg. They concluded that this case further provides evidence supporting the relationship between hepatitis C infection and diverse extrahepatic manifestations, underlying that it is very rare to have pulmonary hypertension, nephrotic syndrome, and polymyositis in a single patient. They included a literature review on the management of several specific extrahepatic manifestations of hepatitis C. The case is well presented and of clinical relevance. However, to further improve the manuscript the authors should expand the relationship between HCV and autoimmunity. It is well-known that HCV may trigger extrahepatic autoimmunity as well summarized in a comprehensive review (HCV and autoimmunity. *Curr Pharm Des.* 2008;14(17):1678-85. doi: 10.2174/138161208784746824.). Importantly, it is well-known that HCV infection is associated to the development of serum autoantibodies, thus potentially causing problems in differential diagnosis when not properly interpreted, as previously reported

(Hepatitis C and autoreactivity. Dig Liver Dis. 2007 Sep;39 Suppl 1:S22-4. doi: 10.1016/s1590-8658(07)80006-5).

**Res:** We appreciate it very much for this good suggestion, and we have done it according to your ideas. As suggested by the reviewer, we have read Ferri's and Bockle's articles in their entirety, and learn a lot from them. According to reference 1 (HCV and autoimmunity. Curr Pharm Des. 2008;14(17):1678-85. doi: 10.2174/138161208784746824), 40-80% of HCV-positive patients develop at least one extrahepatic manifestation during the course of the disease. The majority of these diseases seem to be triggered through autoimmune mechanisms. (Page 7, Line 181-185) According to reference 2 (Hepatitis C and autoreactivity. Dig Liver Dis. 2007 Sep;39 Suppl 1:S22-4. doi: 10.1016/s1590-8658(07)80006-5), HCV infection is often associated with autoimmune diseases such as cryoglobulinemia, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, dermatomyositis, and polymyositis, most of these diseases appear to be related to virus-induced non-specific activation of the immune system, including autoantibody production, cryoglobulinemia, autoimmune thyroid disorders, and B cell lymphomas. (Page 9, Line 241-244).