Dear editor and reviewer,

Thanks for evaluating the manuscript NO: 69882 entitled " Iguratimod in treatment of primary Sjögren's syndrome concomitant with autoimmune hemolytic anemia: a case report". We have modified our manuscript as the reviewer's suggestions point-by-point. As indicated in the responses to the reviewer, we have tried to be responsive to the comments. Our responses to comments of the reviewer as following:

Reviewers' Comments to Author:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

- The term "misdiagnose" (page 8, line 132), which refers to an incorrect diagnosis of an illness or disease, might carry an unnecessary exaggeration. For all we know, autoimmune hemolytic anemia was diagnosed perfectly, and the concomitant Sjögren's syndrome was neglected. Therefore, it might be better to address the Sjögren's as a "missed" diagnosis instead.

Response: Thanks for your professional review. We are sorry for making the mistake. We have rephrased this sentence in the revised manuscript as follows: In this rare case in which the patient did not experience eye and mouth dryness, the initial diagnosis was hyperplastic anemia and AIHA while pSS was missed; however, the patient was finally diagnosed with pSS concomitant with AIHA based on abnormally elevated RF. Please check it (page 8, line 136-139).

- A paragraph should be included in the discussion about the Iguratimod mechanisms of action that were possibly effective in treating this patient (the reason why this agent could be considered as a treatment option for these patients).

Response: Thanks for your professional review. We have rephrased this part in the revised manuscript as follows: Currently, there is no standardized treatment regimen for the treatment of pSS concomitant with AIHA. IGU is a novel anti-rheumatic drug approved only in China and Japan [1,2]. Evidence has shown that IGU can be considered as an effective and safe drug for the clinical therapy of pSS [2]. However, whether IGU can be used for the treatment of pSS concomitant with AIHA remains unknown. In our case, due to the cost of treatment and preventable adverse reactions, the patient received IGU as a second-line treatment under background treatment with a glucocorticoid combined with HCQ. The results showed that the patient responded well to IGU, and her Hb, RET and IgG returned to normal levels during the 24 weeks of follow-up. The following mechanisms might explain the clinical efficacy of IGU in the treatment of pSS concomitant with AIHA. AIHA is a rare autoimmune disease in which autoantibodies directed toward RBC antigens lead to RBC accelerated destruction [3]. Several immunologic mechanisms are involved in the pathogenesis of AIHA, including autoantibodies, antibody-dependent cell-mediated cytotoxicity, phagocytes, B and T lymphocytes, Tregs, cytokines, and the complement system [4]. IGU is an anti-inflammatory and immunomodulatory compound [5]. IGU can significantly inhibit the production of inflammatory cytokines (such as interleukin-6, interleukin-8, and tumor necrosis factor-α) in animal models of arthritis or autoimmune diseases [6]. In addition, IGU plays a significant immunomodulatory role in the synovial tissue of patients with rheumatoid arthritis by regulating T and B lymphocyte subsets and inhibiting the production of cytokines and immunoglobulins [1,7]. Therefore, the improvement in symptoms of patient with pSS concomitant with AIHA might result from the immunomodulation of B lymphocytes. However, the mechanism underlying the clinical efficacy of IGU in the treatment of pSS concomitant with AIHA needs to be determined in further investigations. The present study revealed that IGU was effective for and well tolerated by our patient with pSS concomitant with AIHA. Please check it (page 8-9, line 145-170).

1. Jiang W, Zhang L, Zhao Y, et al. The efficacy and mechanism for action of

iguratimod in primary Sjögren's syndrome patients. International ophthalmology 2020;40:3059-3065

2. Pu J, Wang X, Riaz F, et al. Effectiveness and Safety of Iguratimod in Treating Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis. Frontiers in pharmacology 2021;12:621208

3. Moraes ML, Lima LR, Vicentini-Oliveira JC, et al. Immunosensor for the Diagnostics of Autoimmune Hemolytic Anemia (AIHA) Based on Immobilization of a Monoclonal Antibody on a Layer of Silk Fibroin. Journal of nanoscience and nanotechnology 2019;19:3772-3776

4. Barcellini W. New Insights in the Pathogenesis of Autoimmune Hemolytic Anemia. Transfusion medicine and hemotherapy : offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie 2015;42:287-293

5. Jiang H, Gao H, Wang Q, Wang M, Wu B. Molecular mechanisms and clinical application of Iguratimod: A review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2020;122:109704

6. Xu Y, Zhu Q, Song J, et al. Regulatory Effect of Iguratimod on the Balance of Th Subsets and Inhibition of Inflammatory Cytokines in Patients with Rheumatoid Arthritis. Mediators of inflammation 2015;2015:356040

7. Xie S, Li S, Tian J, Li F. Iguratimod as a New Drug for Rheumatoid Arthritis: Current Landscape. Frontiers in pharmacology 2020;11:73

- What were the limitations of this case report?

Response: Thanks for your professional review. We have added the limitations of this case report in the revised manuscript as follows: There are some limitations in this case report that should be kept in mind. First, the classification of AIHA was not performed in our patient due to hospital condition limitations. Second, the proportion of B lymphocytes was not dynamically monitored during the treatment. Whether B lymphocytes are involved in the possible therapeutic mechanism of IGU in pSS

concomitant with AIHA is not clear. Finally, this case report involved experience with a single patient. Prospective studies with a large sample size are needed to provide more information about the safety and efficacy of IGU in patients with pSS concomitant with AIHA. Please check it (page 10, line 179-186).

- What are the authors' clinical recommendations (diagnosis of similar patients, treatment steps, duration of follow-up, etc.), and suggestions for further research in the field?

Response: Thanks for your professional review. We have added the clinical recommendations in the revised manuscript as follows: Clinicians should be reminded that when hemolytic anemia occurs in young women, they should be alert to the possibility of autoimmune diseases. More comprehensive clinical examination and evaluation, including autoantibodies, immunoglobulins, and complement levels, should be carried out to improve the diagnostic accuracy. The treatment of AIHA should take into account the primary disease, and the dose of glucocorticoids should be gradually tapered. For patients with poor glucocorticoid responses, immunosuppressants should be added as soon as possible. Please check it (page 9, line 171-178). In addition, this case report involved experience with a single patient. Prospective studies with a large sample size are needed to provide more information about the safety and efficacy of IGU in patients with pSS concomitant with AIHA. (page 10, line 183-186).

- The manuscript is well-written; however, I recommend the authors to proofread the manuscript to correct some minor mistakes.

Response: Thanks for your kind review and suggestions. We have rechecked the grammar and spelling of the article. In addition, the revised manuscript has been edited under help of English native speakers (American Journal Experts). We have added the detail in the revised manuscript, and upload the language certificate, please check it.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

This manuscript is well written. But there are some minor issues that need to be addressed. Please discuss the advantages and disadvantages of the diagnosis and treatment of this case and its clinical value. And give suggestions for future research in this field.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Response: Thanks for your professional review. We have added the limitations of this case report in the revised manuscript as follows: There are some limitations in this case report that should be kept in mind. First, the classification of AIHA was not performed in our patient due to hospital condition limitations. Second, the proportion of B lymphocytes was not dynamically monitored during the treatment. Whether B lymphocytes are involved in the possible therapeutic mechanism of IGU in pSS concomitant with AIHA is not clear. Finally, this case report involved experience with a single patient. Prospective studies with a large sample size are needed to provide more information about the safety and efficacy of IGU in patients with pSS concomitant with AIHA. Please check it (page 10, line 179-186).

In addition, we have added the clinical value of this case report in the revised manuscript as follows: Here, we present a rare case of pSS concomitant with AIHA but without eye and mouth dryness that was successfully treated with IGU. To our knowledge, this is the first case report describing the efficacy of IGU in the treatment of pSS concomitant with AIHA, and the findings from this case report indicate that IGU might broaden the treatment options available for patients with pSS concomitant with other rare diseases. Please check it (page 7, line 126-131).

As this study was the experience of a single patient. Prospective studies with a large

sample size are needed to provide more information about the safety and efficacy of IGU in patients with pSS concomitant with AIHA. (page 10, line 183-186).

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, 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. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s). Please add figure(s) to this case report.

Response: Thanks for your professional review. According to your suggestion, we have corrected the Table as the "standard three-line table", please check it (Table 1). In addition, we have upload the approved grant application form or funding agency copy of all approval documents, please check it.

In our case, the diagnosis of PPS concomitant with AIHA mainly depended on the results of laboratory tests. In addition, the detailed results of laboratory tests have been shown in the manuscript. Therefore, no figure related to our case could be displayed in the manuscript. Anyway, we thank for the reviewer's thoughtful advice.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Best regards

Hai-Li Shen