Format for ANSWERING REVIEWERS

April 15, 2015

Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: IgG4 unrelated AIP revise final).

Title: IgG4-unrelated type 1 autoimmune pancreatitis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17141

The following manuscript improvements have been made based on the suggestions of reviewers:

1 The format has been updated.

2 Revisions have been made according to each reviewer's suggestions.

(a) Reviewer 00004525

1. As the ERP finding is level 2, this case is diagnosed as probable type 1 AIP according to ICDC.

-We have diagnosed this case as definitive type 1 AIP based on the histological findings by EUS-FNA. The details are described in the second paragraph on Page 9.

2. Page 9, line 19. Reference number of 10 is wrong.

-We have changed reference number 10 to 13. This correct reference is now on page 14.

(b) Reviewer 00225267

1. In the figure legend, many acronyms were used. Although acronyms were documented with full characters in the main body, it is not desired to use many acronyms in the figure legend.

-As suggested by Reviewer 00225267, we have added the full characters in addition to each acronym in the figure legends.

2. If you have more specific image about localized swelling of the pancreas head in Fig. 2A, please change the image. In present image, "localized swelling of the pancreas head" is not clear.

-To demonstrate the swelling of the head of the pancreas, we have added the CT image obtained after steroid administration.

3. *In the Table 1, please revise Amy as Amylase. And, please consider removal or summary of "Table 1". There are so many results unrelated with "AIP".*

-As suggested by Reviewer 00225267, we have changed "Amy" to "Amylase." Although Reviewer 00225367 suggested that Table 1 should be deleted, we have instead revised Table 1 because Reviewer 03260942 suggested that the normal reference range values should be added to Table 1.

(c) Reviewer 03260942

(Major)

1. The authors mention several concluding statements under various headings (abstract, core tip, introduction, discussion) that are not entirely in sync. For example, in the abstract they mention, "…that the phenotypes of AIP are not associated with IgG4" while in the discussion they state that "the pathogenesis of type 1 AIP is not always associated with the mechanism of overproduction of IgG4." In order to be clearer to the reader, it would be helpful to clarify their overall conclusion in all sections of the paper.

-This case revealed symptoms compatible with type 1 AIP without an elevation of serum IgG4 or IgG4-positive plasma cells infiltration in several organs. This case may demonstrate that even with these symptoms, IgG4 did not contribute to the pathogenesis or mechanism of type 1 AIP. Therefore, we have provided several possible explanations in the manuscript.

2. Some of the high impact publications in the field are not mentioned. I would recommend including several published manuscripts in the literature in adults and a pediatric case of type 1 AIP with normal serum IgG4. These would strengthen the argument for a separate phenotype of type 1 AIP. References below: a. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol 2007;102(8):1646-53. b. Friedlander J, Quiros JA, Morgan T, et al. Diagnosis of autoimmune pancreatitis vs neoplasms in children with pancreatic mass and biliary obstruction. Clin Gastroenterol Hepatol 2012;10(9):1051-5 e1.

-As suggested by Reviewer 03260942, we have added two citations to the discussion of IgG4-negative AIP. This change was made in the first paragraph on Page 10.

3. While the authors have attempted to investigate the pathway by which they describe the pathogenesis of IG4 seronegative AIP, until this is proven it may be more relevant to the reader to limit this discussion to a paragraph within the manuscript.

-The authors agree with the suggestion of Reviewer 03260942. The pathway was a hypothesis to speculate based on other articles. It is very difficult to prove this hypothesis based on a few cases. To help accumulate such cases in the future, we would like to present this case in *WJG*.

4. The case for which hyperproteinemia work up was pursed is not very clear. Please go over the presentation, clinical scenario. Would the authors be able to clarify the manner in which this patient was evaluated for hyperproteinemia? Is the first step always a PET scan or are there other steps in between that would lead one to go down this path?

-We had to rule out multiple myeloma in the process of diagnosis. We have added an explanation as follows: "He was diagnosed with hypergammaglobulinemia, and a bone marrow biopsy and fluorodeoxyglucose (FDG)-positron emission tomography (PET) were performed to rule out multiple myeloma."

5. List what the case fits from the ICDC criteria, after listing the criteria.

-We have added the ICDC list for the present case to the discussion. The details are described on Page 7 and Page 8.

Minor:

1. Under the "Core tip" section, would spell out "RD" as "related disease" for the first time.

- We have changed "RD" to "related disease" in the Core tip.

2. *Towards the end of the introduction the authors state, "However, the role of IgG4 in the phenotypic expression of AIP or IgG4-RD has not been clarified." Please clarify as the ICDC criteria for AIP is very specific on the role of serum IgG4 and histology with respect to IgG4.*
-ICDC are the criteria used for diagnosing AIP. IgG4 is a very important factor for diagnosing type 1 AIP based on ICDC guidance. In fact, AIP cases without an elevation of serum IgG4 or infiltration of IgG4 positive plasma cells can be diagnosed as AIP based on ICDC using other factors such as OOI, response to steroids, pancreatic imaging, and so on. ICDC is not a tool to explain the relationship between IgG4 and the pathogenesis of AIP. In this case, we could not reveal the role of IgG4 to demonstrate the phenotype.

3. Please list normal reference range values in the manuscript and the table.
-We have added the normal reference ranges to Table 1.

4. Please clarify "liver dysfunction" as alkaline phosphatase and GGT are not liver function tests.
-We have changed "liver dysfunction" to "an elevation of ALP and γ -GTP" or "hepatobiliary enzyme".

5. Please define Mikulicz disease.
-We have changed the expression of Mikulicz disease to sialadenitis and dacrioadenitis to avoid confusion.

6. Please share the needle size used to obtain pancreatic tissue via FNA as this would be helpful for others in the field to know.
-We have added a description of the needle size used in EUS-FNA.

7. Please clarify for how long patient was on 30 mg/day steroids, taper duration and duration of maintenance therapy.
8. How long was patient on steroids before labs and imaging were repeated? How did the labs change (values?)
-As suggested by Reviewer 03260942, we have revised the description of the steroid therapy. We also provided the results of the post-steroid therapy examination (new Table 2).

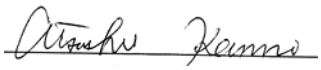
9. Please consider labeling the abnormal portions on your histological pictures to help the reader with arrows. These pictures are great.
As suggested by Reviewer 03260942, we have added arrows to the histological pictures.

10. Back up the CD-3, CD 20 stains initiatives. The main goal and objectives from investigating these pathways.
-As suggested by Reviewer 03260942, the evaluation of specimens from this patient with anti-CD3 and anti-CD20 antibodies was conducted to find out which one had greater activity: B-lymphocytes or T-lymphocytes. This information enriches our knowledge regarding which pathway relates to the IgG4 production pathway: the T cell-dependent pathway or the T cell-independent pathway. Moreover, another reason why this evaluation was conducted was because it was considered that a comparison between the previously reported IgG4 negative AIP case and the present case would facilitate our understanding of the pathological conditions of the present case.

3 References and typesetting were corrected
4 Our manuscript has been checked by a scientific editor at our university. Please find attached the certificate of English editing issued by the scientific editor.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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