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Column: Case Report

Is the simultaneous presence of IgG4-positive plasma cells and giant-cell hepatitis a coincidence in autoimmune hepatitis? A case report and literature review

Point-by-Point Response

Please note that the changes made do not influence the content, conclusions, or framework of the paper. We have not listed below all minor changes made; however, these are indicated in the revised manuscript.

Reviewer #1:

Comments to authors: 1. The title "Is the simultaneous presence of IgG4-positive plasma cells and giant-cell hepatitis a coincidence" was a vaguely raised sentence. It is likely better to add "in AIH".

Response: We have revised the title as follows: "Is the simultaneous presence of IgG4-positive plasma cells and giant-cell hepatitis a coincidence in autoimmune hepatitis"

2. In Abstract, lane 1: In IgG4-AIH, causal association of IgG4-positive plasma cells and liver injury has not yet been demonstrated in the literatures.

Response: We have revised the text as follows: "The immune-mediated invasion of IgG4-positive plasma cells in the liver is found in some cases of autoimmune hepatitis."

3. In Abstract, Conclusion: "AIH with simultaneous IgG4-positive plasma cell infiltration and GCH, liver inflammation, and fibrosis was often more severe" is an overstatement.

Response: We have revised the text as follows: "AIH with simultaneous IgG4-positive plasma cell infiltration and GCH, liver inflammation, and fibrosis may be more severe than typical AIH…"

4. Throughout manuscript: Interfacial inflammation should be corrected to interface hepatitis.

Response: We have modified the text as requested.

5. In Discussion, Reference 5: It was a report for IgG4-positive plasma cell -associated pulmonary inflammation, not for IgG4-related liver disease.

Response: We have deleted inappropriate references.

6. In Discussion, page 2, lane 7-8: Authors should mention the criteria of IgG4-AIH in Reference 16, which was based on the ratio of IgG4-positive plasma cells, being different from the previous criteria.

7. In Discussion, page 2, lane 8-12: Reference number 16 should be inserted to this sentence.

Response: We have added the following text: "The ratio of IgG4-positive plasma cells to plasma cells infiltrated in tissues was > 40%."

8. How frequent was the co-occurrence of typical AIH and GCH? Authors are encouraged to mention and discuss about the relative importance of GCH in IgG4-AIH, comparing to that in classical AIH.

Response: The frequency of GCH in classical AIH has not been reported; however, based upon

our review of the literature, GCH may be related to AIH. We have elaborated on this point in the paper. The relationship of GCH in IgG4-AIH was reviewed in three cases and described in detail in this paper.

9. In Discussion, the last paragraph: "The simultaneous occurrence of IgG4 and GCH in AIH" is inappropriate depiction: Relating to the above comment 7, authors should discuss whether IgG4-AIH and typical AIH are distinct disease entity or within continuing spectrum.
Response: The simultaneous occurrence of GCH and IgG4 plasma cells in AIH is rare and may not be linked; the reported literature contains only case reports. IgG4-AIH is also not recognized by authorities; therefore, it is difficult for us to discuss further.

Reviewer #2:
Specific Comments to Authors: Authors presented a case of IgG4-associated autoimmune hepatitis with concomitant giant cells hepatitis. Despite being an interesting and rare case there are some issues that should be addressed: - Which classification was used to quantify fibrosis? Ishak? Metavir score? Authors says that fibrosis improved – please specify the degree of improvement using a validated classification.
Response: We have added the fibrosis score from 5 points to 2 points using the Ishak fibrosis score. We have added Masson staining images of liver fibrosis from the first and second liver biopsies to better understand the improvement of liver fibrosis; this is shown in Figure 3 B, C.

- Authors concluded that "liver inflammation, and fibrosis was often more severe than typical AIH but sensitive to corticosteroids, and both pathological features disappeared upon treatment" but these conclusions can't be made based only on this case – remove it from abstract section as it seems that it is a conclusion of the case. Furthermore, I think authors should be more cautious and not so assertive in conclusions. For example, 25% of patients did not response do corticosteroids (1 in 4 is not neglectable) – we can only say that it seems to be steroid sensitive in most of cases.
Response: We have revised the Abstract and Discussion: "AIH with simultaneous IgG4-positive plasma cell infiltration and GCH, liver inflammation, and fibrosis may be more severe than typical AIH and more sensitive to corticosteroids."

- The discussion is too long - The phrase "It has been recently reported that in the diagnosis of IgG4-autoimmune hepatitis (IgG4-AIH) [2, 3], that is, in the classic AIH, elevated serum IgG4 and IgG4-positive plasma cells are observed " in introduction makes no sense. Please rewrite it.
- The correct term is interface hepatitis (and not interfacial hepatitis, repeated many times in the manuscript). Please correct.
Response: We have revised the Discussion based on the comments of all the reviewers. The term "interfacial hepatitis" has been replaced with "interface hepatitis."

Reviewer #3:
Specific Comments to Authors: Youwen Tan et al case presented IgG4-related autoimmune hepatitis (IgG4-AIH) accompanied with gait cell hepatitis (GCH). English writing is fair (no grammatical error) and this work is worth enough for possible publication in WJG if some comments listed below are correctly responded. Major comments.

1. The authors need to describe in this case report whether any IgG4-related diseases including IgG4-relatied cholangitis are accompanied with or not. The results of imaging examinations such as MRCP or enhanced CT are necessary.

Response: We have added the following text: "Enhanced upper abdominal CT, magnetic resonance, and magnetic resonance cholangiopancreatography found splenomegaly but no other lesions including lesions of the pancreas and bile duct."

Minor comments.

1. Provide page number in the manuscript. 2. Page 7, lines 13. Uemura is Umemura

Response: We have modified the text as requested.

Reviewer #4:

Specific Comments to Authors: The authors reported a 68-year-old woman who presented IgG4-positive AIH together with giant-cell transformation of a few hepatocytes. Although the authors attempted to evaluate the possibility of simultaneous occurrence of AIH and giant-cell hepatitis, mainly based on the literature search, their conclusions seemed to be ambiguous. The reviewer is wondering whether the authors have just wanted to document that presence of giant-cell transformation of hepatocytes might solely reflect severity of inflammation due to AIH. The authors had better describe more clearly what they want to propose in this interesting case report.

Response: We have found an interesting case of the co-existence of GCH and IgG4 in AIH. We tried to explain the mechanism, but we could not find a good potential pathogenesis based on our review of the literature. We hope to have the opportunity to conduct further studies in the future.

Reviewer #5:

Specific Comments to Authors: The authors presented a rare case of 68-year-old woman with IgG4-associated autoimmune hepatitis combined with giant-cell hepatitis. Methylprednisolone treatment improved liver inflammation and fibrosis, as proved by a second liver biopsy. The authors then reviewed the literatures reporting similar pathological phenomena. The simulataneous presentation of IgG4-AIH and GCH was very rare and they analyzed the possible reasons for its appearance. Both the scientific quality and the language quality of this manuscript were good. I have a few suggestions which may improve the manuscript.

1, please label the scale bars in Figure 2 & 3.

Response: We have revised the figures accordingly.

2, Fig.2B was stated as "400X magnification". However, the nuclei in Fig.2B seemed the same size as in Fig. 2A (200X magnification) and much smaller than Fig. 2C&2D (both in 400X magnification). I think the authors made a wrong labelling of magnification of Fig. 2B and I suggest them use a new one with real 400X magnification so that the readers may better view the giant cell hepatitis.

Response: We have replaced Figure 2B to better demonstrate the GCH (400× magnification).

3, For better appreciation of thinner fiber spacing and improvement of fibrosis, I would suggest the authors provide a Masson staining of the first liver biopsy specimen. 4, please refer in the manuscipt where it applies as Fig. 2A, 2B, 2C or 2D, instead of using Fig.2 as an overall representation. The same situation happens to Fig. 3.

Response: We have added a Masson staining of the first liver biopsy specimen (Figure 3B) and revised the figure labels accordingly.

Reviewer #6:

Specific Comments to Authors: This manuscript is interesting and well-written. However, the quality of IgG4 staining is not sufficient. Please replace the original figure with a high quality one.

Response: We have replaced the image so that more IgG4 positive plasma cells are visible (Figure 2D).

Second-Round Review

Reviewer #1:

Specific Comments to Authors: Authors addressed the majority of comments. However, in my opinion, discussion is still too extensive - it is difficult to stay focus and understand what authors really want to discuss. Authors should reduce this section and be more clear about what they want to emphasise with this case (there's not a clear message).

Response: We have revised the Discussion to be more clear about what they want to emphasise with this case.