Sep. 6, 2018

Re: WJCC-MS-41042R1

Responses to reviewers' comments

Reviewer #1:

The authors thank the reviewer for his/her efforts and valuable time in reviewing on our manuscript. Your comments are very helpful for improving the quality of manuscript, and of course they were very encouraging. We have made significant changes in revision based on your constructive suggestions and comments from other reviewers, by adding an image for IgG4 IHC staining to show IgG4-positive cell infiltration in bladder mucosa, shorting the length of main text, and correcting the grammar errors and typos in the revision, and stating our finding properly. Below our response your concerns, and we marked the changes in color font. Again, thank you very much.

Comments

The manuscript by Jing Xue et al describes a case report for IgG4-related progressive multi-organ disease. The manuscript is clearly written and very nicely reflects the relationship between IgG4 levels and the clinical condition. Title, abstract, and keywords are all consistent with the findings described. The introduction adequately describes the background and the significance of the study. Methods are clear and results are complete and well presented. Discussion section is clear and very informative. This is a very nice report that provides attention to an uncommon but relevant immune disease with multiple clinical manifestations. Just a couple of minor points: In page 3 "She was first diagnosed was "allergic rhinitis" and was externally treated…" It should be She was first diagnosed with "allergic rhinitis" and was externally treated… According to the SI units, the symbol for liter is small l, not capital L. this should be corrected.

Response:

Thank you for your encouraging comments. We have corrected the typo "She was first diagnosed was "allergic rhinitis" and was externally treated…" It should be She was first diagnosed with "allergic rhinitis" and was externally treated… In page 3, and the symbol for liter using low case "l" instead throughout the text.

Reviewer #2:

We thank the reviewer for his/her efforts and valuable comments on our manuscript. These comments are very helpful for improving the quality of manuscript. We have made significant changes in revision based on your constructive suggestions, by adding an image for IgG4 IHC staining to show IgG4-positive cell infiltration in bladder mucosa, shorting the length of main text, and correcting the grammar errors and typos in the revision, and stating our finding properly. Below are the point-to-point responses (R) to your itemized concerns (C), and we marked the changes in color font.

Comments (C)

C1. I think the case itself is interesting but the discussion improved and other points addressed. IGG4RD isn't that novel but there are some interesting aspects to this particular case. Spelling, grammar, English expression throughout needs to be addressed – recommend they get the paper edited Discussion could be improved, see comments.

R1. Thank you for your valuable comments. We extensively edited the text in the revision. The language was improved.

C2. Also they need to emphasise how their patient fits this diagnosis, what was different, what makes this case unusual/interesting rather than leaving the reader to draw this conclusion.

R2. This case has been misdiagnosed for over 15 years, and several organs were involved before she was treated for IGG4RD. We emphasized this progressive development of multiple organ involvement in the revision. Thank you.

C3. This section needs to be improved-focus on the pathophysiology of IGG4RD rather than general basic immunology. Some key laboratory investigations (in my opinion!) are missing - i.e. one would imagine they would have done an EPG for IgG paraprotein, also they don't mention any autoantibody testing (ie relating to Sjogrens etc) - even though it does look like IGG4RD, they should mention these relevant negative findings

R3. Thank you for these important comments. All pathophysiology of IGG4RD-related data were presented in tables, we did not do an EPG for IgG paraprotein. Our diagnosis of IGG4RD was first based on the elevated IgG4 level in the plasma and the efficacy of steroid treatment. We have added more detailed lab data in table 1 with autoantibody testing.

C4. They need to expand on their histological features on the biopsy - did it meet criteria for a diagnosis of IGG4RD? If they have photos, this should be added to the paper

R4. Since we missed to collect biopsy from this patient in her previous visits but the latest visit because of symptoms of polydipsia and polyuria, burning and pain. The biopsy of bladder mucosa was collected and IHC for IgG4 was performed, this image was incorporated in Fig. 4B. The image showed a detectable level of IgG protein and IgG4-positive cell infiltration in bladder mucosa biopsy.

C5. The results table should be re-organised as mentioned in the comments Page 2, line 10: 'lymphoplasmacytic infiltration' But did this meet the histopathological criteria for diagnosis of IGG4RD, i.e. positive IGG4 staining on immumohistochemistry?
R5. The results table was reorganized. Since we didn't do IgG4 staining for ymphoplasmacytes, we did not have data to state if this met the histopathological criteria for diagnosis of IGG4RD at this point. Thanks for this critical comment.

C6. Page 2, line 18: 'multi-organ involvement'. This is not and ideal keyword.
R6. Thank you for this valuable suggestion. We used "steroid therapy" instead of "multi-organ involvement" as a keyword.

C7. Page 3, Line 24: 'rib gracture' Was this a traumatic rib fracture? Did she have investigation for a paraprotein? DDx plasma cell dyscrasia with Igg4 paraprotein.
R7. Yes, it was the traumatic rib fracture. We corrected it in the revision. We did not conduct an investigation for a paraprotein.

C8. Page 3, line 29: 'a paste' ointment?
R8. Yes, we change it as "an ointment" accordingly in the revision. Thank you.

C9. Pahe 4, lines 20-22: Better to give absolute numbers as well as percentages.
R9. The absolute numbers were added in the revision and/or the tables. Thanks.

C10. Page 5, line 4: 'Sjoren's syndrome', Any ANA/ENA results?
R10. For consideration of 'Sjoren's syndrome', it was based on the pathology of labial gland biopsy that showed lymphoplasmacytic infiltration into the focal lobules of the salivary gland tissue beneath the squamous mucous epithelia, with low level of serum complement C3, positive HEp2-ANA 1:100 (<1;100), but negative ENA-AbSSA: negative, ENA-AbSS. We included this lab data in revised table 1. Thank you.

C11. Page 6, line 19: Confirmatory testing is histological.

R11. Thanks for clarifying. We changed this statement as "The patient was thus diagnosed as IgG4-RD suspicious".

C12. Page 8, 2nd last sentence: How did your patient fulfil these criteria?
R12. Since we missed most windows for histological examinations, and the last two criteria, i. e. (3) the histological pattern of lesions is fibro-inflammatory, with a lymphoplasmocytic infiltration of IgG4-positive plasma cells and storiform pattern of fibrosis, and the ratio of IgG4/IgG-positive plasma cell is above 40% in tissues; and (4) immunohistochemistry showed more than 10 IgG4-positive plasma cells per high powered field (HPF) have not been performed, we stated this case as "In this case, the patient at least fulfills two of above criteria, 1) one or more organs experience diffuse/focal swelling and serum IgG4>135 mg /dl, and therefore was diagnosis as diagnosed as IgG4-RD suspicious" in the discussion accordingly. Thank you.

C13. Table: Recommend re-organising the table, grouping together laboratory/radiographical/clinical features rather than chronological list. Can still give the years but rearrange. Was ANA, ENA done? Evidence of autoantibodies associated with Sjogrens. 2006.3.31
R13. Thank you for this constructive suggestion. Since this is a case with a long-term of 19 years with different symptoms each times, there are so many clinical data of examinations, and the case was described by times far to near, we think it may be easier for readers to follow by reading the table organized by time. Ttherefore we hope to keep the same format and style.

C14. Biopsy: More details needed here, consider photographs of histological findings. 2009.11.13: give absolute numbers as well 2011.11.22: Did you ever do protein electrophoresis for a paraprotein? If so, document this also.
R14. These are all critical comments. Since we missed to collect biopsy from this patient in her previous visits but the latest visit because of symptoms of polydipsia and polyuria, burning and pain. The biopsy of bladder mucosa was collected and IHC for IgG4 was performed, this image was incorporated in Fig. 4B. The image showed a detectable level of IgG protein and IgG4-positive cell infiltration in bladder mucosa biopsy. Sorry we did not perform protein electrophoresis for a paraprotein. Thank you.

Reviewer #3:

The authors thank the reviewer for his/her time and suggestive comments on our work. Your comments are very valuable for improving the quality of manuscript. We have made significant changes in revision based on your constructive suggestions, by adding an image for IgG4 IHC staining to show IgG4-positive cell infiltration in bladder mucosa, shorting the length of main text, and correcting the grammar errors and typos in the revision, and stating our finding properly. Below are the point-to-point responses (R) to your itemized concerns (C), and we marked the changes in color font.

Comments

This is a case report regarding the multi-organ involvement of IgG4-related disease taking over 19 years for definite diagnosis. Although the case itself is interesting, I have some major comments.

C1. First, the manuscript is too long as a single case report. Especially, case presentation is too long and too complicated. The readers would feel hard to understand the case. The authors should extensively revise their manuscript more shorten, more simplify and more summarized.

R1. Thank you for this constructive suggestion. We have extensively edited the text by reducing grammatical errors and typos, shorting the length of text in the revision.

C2. Table 1 is too busy and complicated. Only significant and important information should be summarized as Table. The details of date should be noted in manuscript only if it is absolutely important.

R2. The table 1 was re-organized according to the suggestion by Reviewer #2. Thank you.

C3. The authors should present some pathological photographs showing lymphoplasmacytic infiltration and immunohistochemistry of IgG4.

R3. Thank you for your critical comment. Since we missed to collect biopsy from this patient in her previous visits but the latest visit because of symptoms of polydipsia and polyuria, burning and pain. The biopsy of bladder mucosa was collected and IHC for IgG4 was performed, this image was incorporated in Fig. 4B. The image showed a detectable level of IgG protein and IgG4-positive cell infiltration in bladder mucosa biopsy.