Author’s response to reviews

Title: Simultaneous Occurrence of IgG4-related Tubulointerstitial Nephritis and Colon Adenocarcinoma with Hepatic Metastasis: A Case Report and Literature Review

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Author’s response to reviews:

Dear Editor,

Re: BNEP-D-18-00470R1

Title: Simultaneous Occurrence of IgG4-related Tubulointerstitial Nephritis and Colon Adenocarcinoma of Colon with Hepatic Metastasis: A Case Report and Literature Review

Authors: Shen-Ju Gou; Lu-Jia Xue; Zhang Xue Hu

Thank you for giving us an opportunity to revise our above referenced manuscript. We have revised the manuscript carefully according to the Editor’s and Reviewers’ comments and recommendations. The revision was highlighted in red in the text according to your requirement. In brief, the revision includes the following changes:

1. The manuscript has been copy-edited by a native English speaker.

2. Summary of previous reports of malignancies associated with IgG4 tubulointerstitial nephritis was added in the form of a table. We added “and literature review” to the title of the manuscript accordingly.

3. The contribution of this case report was explained in the response to reviewer 2.

The response to each question or comment of the reviewers is listed point-by-point in the attached pages. We hope the revised form is suitable for publication in your journal.

Thank you for your consideration.

Yours sincerely,
Zhang-Xue Hu

Answer to the comments from the Editor:

Please copy-edit your manuscript, we suggest you ask a native English-speaking colleague to help you with this. In addition, please make the contribution this case report represents very clear in your response to reviewer 2.

Answer: Thank you very much for the comments. Mistakes in English grammar have been corrected, and the manuscript has been copy-edited by a native English speaker. We presented the contribution of this case report in our response to reviewer 2.

Answer to Reviewer 1

Major points

1. Please detail the treatment given for the colon adenocarcinoma.

Answer: The patient was diagnosed as colon adenocarcinoma with hepatic metastasis. The therapy decision made by the oncologist for the adenocarcinoma of this patient was chemotherapy. However, the rapid rise in serum creatinine level indicated deteriorated renal function. The severe impaired renal function is the contraindication of chemotherapy. The renal biopsy revealed IgG4-related tubulointerstitial nephritis in this patient, so we tried to treat the patient with prednisone to improve kidney function and to create better conditions for the chemotherapy. Although his renal function improved with prednisone, the patient died at home during the waiting period for chemotherapy. The explanation of the treatment given for the colon adenocarcinoma have been added in the text according to the recommendation.

2. Please detail the circumstances and cause of death of the patient.

Answer: The patient was followed up regularly in the out-patient department. After the treatment of prednisone, the renal function improved and the general condition of the patient got better for five months. However, later on, the general condition of the patient deteriorated quickly. The patient suffered from anorexia and poor mental state. The last follow-up, which happened two days before the death, the patient experienced a shortness of breath. The patient refused the hospitalization suggestion from the doctor and died two days later. The last serum creatine level tested was 176 μmol/L. For the cause of the death, we could not draw a definite conclusion but we inferred that infection might play a role. Some of the data described above have been added in the text according to the recommendation.

3. Please provide a table or similar summarising previous reports of both primary and metastatic malignancies associated with IgG4 tubulointerstitial nephritis. This manuscript is as much an opportunity to highlight this interesting case as it is to summarise all similar reported cases of simultaneously occurring or paraneoplastic IgG4
tubulointerstitial nephritis. Whilst the case report is well depicted, the summary of previous cases is not as strong as it should be in order to inform the readership and provide the addition value that should be provided.

Answer: Thank you for the comment, and we agree with that. We summarized previous reports of malignancies associated with IgG4-related tubulointerstitial nephritis in the form of a table. There were five case reports. We added the description to the second paragraph of the discussion and conclusion section as follows: IgG4-RD involved potentially every organ or system, occasionally including kidney. It was reported that nearly 30% of the IgG4-RD might have tubulointerstitial nephritis. The association of IgG4-TIN and malignancy was described in several isolated case reports, which was summarized in Table 1.

Minor points

1. Attention to English language, especially tense, spelling (crucial rather than crutial) and pronouns.

Answer: Thank you for the comments. Mistakes in English language have been corrected, and the manuscript has been revised by a native English speaker.

2. Please clarify what is meant by the 3rd and 4th sentences in the second paragraph on page 6 (ie, last paragraph before Discussion & Conclusions).

Answer: Thank you for the comments. The sentence mentioned above was used to explain why the treatment decision was made. Since the patient was diagnosed as IgG4-related tubulointerstitial nephritis and colon adenocarcinoma. The nature of liver nodules was not clear at that time. They might be IgG4-related pseudo-tumor or metastasis of colon adenocarcinoma. Since the renal dysfunction provided limitation for the treatment of colon adenocarcinoma. So we firstly chose to treat IgG4-related tubulointerstitial nephritis with prednisone. Prednisone of 1 mg/kg daily was initiated with the objective to treat IgG4-TIN. On the one hand, the treatment might improve renal function, the improvement of renal function would then create better conditions for chemotherapy or surgery of adenocarcinoma treatment. On the other hand, the imaging response of hepatic nodules to glucocorticoid administration might suggest whether the nodules were malignancy or IgG4 related pseudo-tumor. It has been revised accordingly in the manuscript.

3. Please be more specific in regards to the proportions and numbers of previously reported cases in the first paragraph on page 8 (commencing with "A fair proportion of...")

Answer: We agree with your comment. The proportions and numbers of previously reported cases have been added according to the recommendation.

Answer to Reviewer 2
1. This association has been reported in several cohorts of patients with cancer diseases, including the colon. The fact that IgG4-related TIN was diagnosed, while the patient developing metastasis does not in any way mean a relationship between the two pathological events, but rather with immune disorders associated with malignancy process. The authors should modify their comments accordingly.

Answer: Yes, we agree with your comment. It is true that the association has been reported in several cohorts of patients with cancer diseases, including the colon. For the present case, the metastasis of malignancy did not mean a relationship between the metastasis and IgG4-TIN. The description “metastasis of malignancy associated IgG4-related disease” in the manuscript was not accurate. We modified it as “metastasis of malignancy occurred simultaneously with IgG4-TIN” according to the comment. The similar descriptions in the manuscript were all revised accordingly.

2. Although the IgG4 level decreases significantly upon steroid therapy, only partial recovery of renal function was observed. A better description of renal histological findings, including Masson's trichrome stain and low magnification of renal tissues are required. Immunofluorescence findings were not reported.

Answer: Yes, we totally agree with your comment. Although the IgG4 level decreased significantly upon steroid therapy, only partial recovery of renal function was observed in the present case. This might be partially explained by the findings in renal histology. Under low magnification, the light microscopy demonstrated glomerular sclerosis in two of twelve glomeruli. The other glomeruli demonstrated mild lesion. The periodic acid-silver metheramine and Masson's trichrome staining showed 75% interstitial fibrosis and tubular atrophy in the tubulointerstitial area. In the fibrotic interstitial compartment, collagen fibers exhibited a storiform pattern, with massive lymphocyte and plasma cells infiltration. Immunohistochemical staining showed more than 30 IgG4-positive plasma cells per high-power field (HPF). Immunofluorescence testing was negative for IgG, IgA, IgM, C3, C4, C1q, κ chain, and λ chains in glomeruli. A diagnosis of IgG4-related tubulointerstitial nephritis was thus made. The description in the manuscript has been revised according to the recommendation. The pictures of Masson's trichrome stain were added to the figure 2.

3. Please precise the renal function one year before. The sentence "The renal function was normal" is not acceptable. Because patient exhibited "normal" renal function one year before, how to explain only partial renal recovery after steroid therapy?

Answer: Yes, the serum creatinine level (101μmol/L) one year before was added in the manuscript according to the recommendation. After steroid therapy, the serum creatinine level had been decreasing. The serum creatinine level was 176 μmol/L before the death of the patient, which was still higher than the baseline one year before. Steroids generally leads to rapid and consistent remission of IgG4-TIN. But renal function did not recover completely in patients with advanced renal damage(Kidney international, 84 (2013) 826-833). The incomplete renal recovery might partially attribute to the severe interstitial fibrosis and tubular atrophy in histology.
4. The normal values of biological tests should be added.

Answer: Yes. The normal values of biological tests have been added according to the recommendation.

5. How to explain dysuria without obstructive nephropathy?

Answer: The patient was suffered from the discomfort of benign prostatic hyperplasia one year ago. The dysuria could be explained by the obstruction of prostate enlargement of the lower urinary tract. The radiologic data did not reveal the evidence of prostate involvement of IgG4-RD. We did not perform prostate biopsy. Since the description by the word dysuria might confuse readers, we revised it as detailed description as urinary hesitancy, dribbling urination, and prolonged urination in the manuscript.

6. Regarding the abstract of Feng YL's paper (written in Chinese), what this case-report brings in more?

Answer: In the paper written by Feng YL, et al., they reported nine IgG4-RD patients with malignancies. The leading type of the malignancy was colorectal malignancy, with 3 out of 9 patients were diagnosed. The primary organ with malignancy, colon, in the present case, was the same as the paper written by Feng YL, et al.. However, the present case still had several differences from the previous reports. The malignancy reported in the paper written by Feng YL, et al. were primary malignancies. The present case reported a simultaneous occurrence of metastasis and IgG4-RD, which added the knowledge that IgG4-RD could occurred in the metastasis stage of malignancy. The differential diagnosis of the liver nodules in the present case was difficult, but interesting and with clinical significance. In addition, IgG4-RD reported in the paper written by Feng YL, et al. involved more than 2 organs in all patients, of which the most often involved organs were pancreas (8/9). The IgG4-RD in our case has no evidence of IgG4 involvement in the pancreas or digestive tract, only involving the kidney. This different organ involvement mode of IgG4-RD might be added to the knowledge of IgG4-RD occurred concurrently with malignancy.