Author's response to reviews

Title: A case of IgG4-related kidney disease from the renal pelvis mimicking urothelial carcinoma

Authors:

Hui Zhang (moshanghuizi@126.com)
Xinyu Ren (renxinyu7957@163.com)
Wen Zhang (lovemexieh@126.com)
Di Yang (punchzhanghui@126.com)
Ruie Feng (fengruie1@163.com)

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Author's response to reviews: see over
RESPONSE LETTER

Title: A case of IgG4-related kidney disease from the renal pelvis mimicking urothelial carcinoma

Author(s): Hui Zhang et al.

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Email address: moshanghuizi@126.com; fengruie1@163.com

Full postal address: Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, PR China.

Phone: +8601069159374

Dear editor and reviewers,

We highly appreciate you for reviewing our paper. We have seriously addressed your valuable comments by point-to-point responses and listed all amendments in the following context. We also have made revisions according to the comments in the revised manuscript. Thank you so much.

Yours sincerely,

Hui Zhang
Response to each reviewer's comments

REFEREE COMMENTS

Reviewer: 1

Comments to the Author

This is an interesting differential diagnosis of upper tract filling defect. A few points need to be addressed.

MAJOR REVISIONS

(1) The authors need to provide a clear background on IgG4 related disease including clearly stating the organs it typically affects, and how frequently.

Response:

According to your kind suggestion, we have added “This disease manifests as organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously due to marked infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis.” (Page 2, line 51-54), and” Few data exist on the epidemiological and clinical features of large series of patients. The mean age at diagnosis of the reviewed cases was 65 years, and 73–87% are men [8]. IgG4-RKD common and predominantly involves the cortex of the kidney” (Page 2, line 58-60) in the Background section.

(2) The figure does not show the urogram phase of the CT scan which is typically needed for assessment of upper tract pathology. Also, ureteroscopy was considered in the workup?

Response:

According to your kind suggestion, we have added the CTU in figure 1. We could not show the result of ureteroscopy, because it was not performed.

(3) Are there any features or clues that point to the benign etiology of this condition? For example, in the CT the lesion appears very smooth- is this typical of the IgG4 upper tract lesions reported in the literature. Are there any constitutional symptoms associated with the disease entity. What is the differential diagnosis of other inflammatory diseases that present in a similar fashion?

1) Are there any features or clues that point to the benign etiology of this condition? For example, in the CT the lesion appears very smooth- is this typical of the IgG4 upper tract lesions reported in the literature

Response:

CT is most useful in delineating the characteristics and distribution of the renal lesions. Renal pelvic lesions are always encountered as a diffuse thickening of the renal pelvis wall with smooth intraluminal surface during systemic evaluation of IgG4-RD by CT.

2) Are there any constitutional symptoms associated with the disease entity.

Response:

Hypocomplementaemia and elevated serum IgG level are characteristic features of IgG4-RKD. Elevated serum IgG and IgG4 have been found in all patients, but none of them have hypocomplementaemia in these 7 patients including our case. Although hypocomplementaemia is a distinct feature of IgG4-RD, a relatively low proportion of patients actually have it.

3) What is the differential diagnosis of other inflammatory diseases that present in a similar fashion?

Response:

The most common feature of the renal involvement in IgG4-RD is tubulointerstitial nephritis (TIN) with abundant IgG4-positive plasma cells, but glomerular lesions such as membranous glomerulonephritis have also been described. Besides, inflammatory pseudotumors arising in the renal
pelvis is one of the differential diagnosis

**Reviewer:** 2

Comments to the Author

**Major Compulsory Revisions:**

1. Please discuss the role of biopsy in these patients
   
   **Response:**

   According to your kind suggestion, we have added "Takahashi and his colleagues [17] also found that lesions in three patients with IgG4-TIN without steroid treatment or surgical resection progressed, and all patients with IgG4-TIN who underwent steroid treatment had regression of the lesions. These indicate that effective interventions should start as soon as possible for irreversible fibrosis in IgG4-RKD, and steroid treatment has remarkable effect in this kind of disease, at least in the short term, it is vital to avoid unnecessary surgery. CT-guided biopsy or laparoscopic biopsy of the original tumor might help to rule out malignancy." (Page 5, line 141-148)

2. Please discuss the followup for these patients as well as workup for any other systemic manifestations
   
   **Response:**

   According to your kind suggestion, we have added “patients with IgG4-RKD arising from renal pelvis were treated according to different strategies, including surgical treatment alone for 2 patients, steroid therapy alone for 2 patients and surgical and steroid treatment for remaining 2 patients. The renal lesions improved or resolved after the steroid treatment in 3 patients who got steroid treatment (Table 1).” (Page 4-5, line 137-141).

3. Please discuss the long term sequelae of these patients if left untreated also if treated.
   
   **Response:**

   According to your kind suggestion, we have added “Recent studies have revealed several characteristic clinical features of IgG4-RKD, including predominance in middle-aged to elderly men, frequent association with IgG4-RD in other organs, high levels of serum IgG and IgG4, and a good initial response to corticosteroids. However, longer follow-up data for IgG4-RKD, including relapse information, are still sparse. Takako Saeki and his colleagues [18] retrospectively analyzed the longer-term clinical course of 43 patients with IgG4-TIN in detail in a larger cohort, including the responses to corticosteroid therapy, which was the largest series on the long-term outcome of the corticosteroid treatment of IgG4-RKD. They showed that one month after the start of treatment, most of the abnormal serology and radiology parameters had improved, and relapse of IgG4-related lesions occurred in 8 of 40 treated patients. Their studies indicate that the response of IgG4-RKD to corticosteroids is rapid, not total and irreversible lesions may remain, especially in patients with advanced renal damage. Although spontaneous improvement of renal lesions can occur in IgG4-TIN and the indications for corticosteroid therapy in IgG4-RKD have not been established, patients with renal dysfunction should receive it, and careful attention should be paid to renal function during follow-up without therapy [18,19]. A large-scale prospective study is necessary to determine a more useful treatment strategy for IgG4-RKD.” (Page 5, line 149-167)

4. Some include some pathological histological pictures of the tumor
   
   **Response:**

   According to your kind suggestion, we have added the picture of the tumor as figure 2
Minor Essential Revisions
Some include some histological pictures

Response:
According to your kind suggestion, we have added the pictures of the tumor as figure 2
List of Amendments

1. Page 2, line 51-54: insert “This disease manifests as organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously due to marked infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis.”

2. Page 2, line 58-61: insert “Few data exist on the epidemiological and clinical features of large series of patients. The mean age at diagnosis of the reviewed cases was 65 years, and 73–87% are men [8]. IgG4-RKD common and predominantly involves the cortex of the kidney.”

3. Page 4, line 103-107: invert “Hypocomplementaemia and elevated serum IgG level are characteristic features of IgG4-RKD. Elevated serum IgG and IgG4 have been found in all patients, but none of them have hypocomplementaemia in these 7 patients including our case. Although hypocomplementaemia is a distinct feature of IgG4-RD, a relatively low proportion of patients actually have it.”

4. Page 4-5, line 137-148: invert “patients with IgG4-RKD arising from renal pelvic were treated according to different strategies, including surgical treatment alone for 2 patients, steroid therapy alone for 2 patients and surgical and steroid treatment for remaining 2 patients. The renal lesions improved or resolved after the steroid treatment in 3 patients who got steroid treatment (Table 1). Takahashi and his colleagues [17] also found that lesions in three patients with IgG4-TIN without steroid treatment or surgical resection progressed, and all patients with IgG4-TIN who underwent steroid treatment had regression of the lesions. These indicate that effective interventions should start as soon as possible for irreversible fibrosis in IgG4-RKD, and steroid treatment has remarkable effect in this kind of disease, at least in the short term, it is vital to avoid unnecessary surgery. CT-guided biopsy or laparoscopic biopsy of the original tumor might help to rule out malignancy.”

5. Page 5, line 149-167: insert “Recent studies have revealed several characteristic clinical features of IgG4-RKD, including predominance in middle-aged to elderly men, frequent association with IgG4-RD in other organs, high levels of serum IgG and IgG4, and a good initial response to corticosteroids. However, longer follow-up data for IgG4-RKD, including relapse information, are still sparse. Takako Saeki [18] retrospectively analyzed the longer-term clinical course of 43 patients with IgG4-TIN in detail in a larger cohort, including the responses to corticosteroid therapy, which was the largest series on the long-term outcome of the corticosteroid treatment of IgG4-RKD. They showed that one month after the start of treatment, most of the abnormal serology and radiology parameters had improved, and relapse of IgG4-related lesions occurred in 8 of 40 treated patients, suggesting that the response of IgG4-RKD to corticosteroids is rapid, not total and irreversible lesions may remain, especially in patients with advanced renal damage. Spontaneous improvement or remission has been documented in IgG4-RD, spontaneous improvement of radiologic parameters can also occur in IgG4-TIN[18,19]. Although the indications for corticosteroid therapy in IgG4-RKD have not been established, patients with renal dysfunction should receive it, and careful attention should be paid to renal function during follow-up without therapy. A large-scale prospective study is necessary to determine a more useful treatment strategy for IgG4-RKD.”

6. References: adjust to the correct format for this journal.

7. Table: invert “Hypocomplementaemia” column and “Findings at Follow-up” column (Page 8, table 1).

8. Figure 1: invert CTU.