Author's response to reviews

Title: Successful treatment of highly advanced immunoglobulin G4-related kidney disease presenting renal mass-like regions with end-stage kidney failure: a case study

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Hayley Henderson
Executive Editor
BMC Nephrology
Dear Ms. Henderson,

I, along with my coauthors, would like to ask you to consider the revised manuscript entitled “Immunoglobulin G4-related kidney disease with end-stage kidney failure and atypical radiological findings: a case study” for publication in BMC Nephrology as a case report. We thank you and reviewers for comments and suggestions which were helpful in our revision of manuscript.

As reviewer 1 recommended, we added the prednisone taper schedule in case presentation. As reviewer 2 suggested, we deleted the description "a slow progression of kidney failure" and changed the description "IgG4-positive lymphocyte infiltrate" to "IgG4-positive plasma cell infiltrate". In addition, we revised the evaluation of MRI finding which reviewer 2 pointed out. This is one of the most crucial points in this case. According to reviewer 2, we reevaluated imaging results and revised the discussion. We believe this revision makes our report more convincing and increases the significance as evidence of IgG4-related disease.

Below is a point-by-point response to the reviewer’s comments that highlights the changes made in the revised manuscript.

I added co-authors: Fumi Kishi and Seiji Kishi. They contributed the discussion.

Taichi Murakami and Akira Mima are double corresponding authors.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Taichi Murakami and Akira Mima

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REVIEWER 1:

We are grateful to Reviewer 1 for the useful suggestions that improve our paper. We have taken these suggestions into account in the revised paper.

“This is a clearly written case report and the images are excellent. The authors make two important points: (1) treatment with steroids may be beneficial even when the patient presents with uremia and requires dialysis; and (2) results of imaging studies may be different than
reported previously. More detail on the prednisone taper schedule the patient received would be welcomed.”

Response: We have written the prednisone taper schedule in the section of “Case presentation as follows: “He received 50 mg oral prednisolone. With a subsequent decrease of serum creatinine and IgG4 levels, prednisolone was decreased by 2.5 to 10 mg every two to four weeks after induction therapy for 6 weeks. Finally he received maintenance therapy with 5mg of prednisolone 6 months after initiation of treatment.”

REVIEWER 2:

We are grateful to Reviewer 2 for the reasonable and adequate suggestions that improve our paper. We have taken these suggestions into account in the revised paper.

1 “Although the authors assert that high intensity lesions on T2-weighted MR imaging are lesions of IgG4-related kidney disease, this is hardly acceptable because renal function is disproportionately low in comparison with the distribution of restricted high intensity lesions on T2-weighted MR imaging in this case. Rather diffuse low intensity lesions seem to be lesions. Previous reports also have shown that affected lesions in IgG4-related tubulointerstitial nephritis are depicted as hypointense areas on T2-weighted images (Kim B et al. Eur J Radiol 2014;83:1057-62; Inoue D et al. book "IgG4-related disease" Tokyo: Springer Japan; 2014. pp. 99-105). Moreover, the authors noted the follow-up imaging findings to show bilateral global kidney atrophy. To clarify the extent of lesions and to confirm whether high intensity lesions on T2-weighted MR imaging are IgG4-RD lesions or not in this case, a comparison of MRI findings (or CT findings) before and after corticosteroid therapy is recommended.”

Response: Thank you so much for a reasonable comment. This discussion is one of the most critical points in our paper.

First, by ecography, our patient showed mass-like lesions (Figure1) which looked to correspond to high intensity sites on T2-weighted MR imaging. Second, signal intensity of normal kidney cortex is usually lower than that of fat on T2-weighted MR imaging. In this case, however, high-intensity regions of kidney show same with that of surrounding fat. We confirmed high-intensity signal of kidney both by fast spin echo method and by heavy T2-weighted MR imaging. So we speculated that high intensity sites may be abnormal lesions and that this resulted from highly fibrotic TIN with a compositional change of cellular density and fibrosis with increased fluid. In addition, we do not assert that low intensity sites on T2-weighted MR imaging are normal kidney. Honestly speaking, we had no idea which part of kidney specimen of biopsy was obtained from. Based on these reasons we speculated that high intensity sites on T2-weighted MR imaging may be highly advanced lesions of IgG4-RKD, although we did not determine the distribution of lesions.

According to Reviewer 2, we reevaluated imaging results. At the time of admission, bilateral kidneys look a little atrophic, rather than swollen. However, some parts of kidney look mass-like regions by echography, CT and MRI. After steroid treatment, kidneys resulted in focal atrophy
with partial mass-like regions, rather than global atrophy. These partial mass-like lesions, before and after treatment, correspond to high intensity sites on T2-weighted MR. As Reviewer 2 indicates, based on clinical course and imaging results before and after treatment, it is reasonable that diffuse low intensity and high intensity parts are lesions and normal kidney, respectively. We also agree with this point. Previous papers report that distribution of parenchymal kidney lesion is categorized as follows: 1) multiple patchy or wedged lesions, 2) diffuse lesions and 3) tumor-like lesions. Patchy lesions demonstrate convex shape when TIN is severe. Patients with diffuse lesions often show swollen kidney with kidney failure. These findings suggest that our patient showed end stage kidney disease with relatively atrophic kidneys because of highly advanced multiple patchy lesions of IgG4-RKD, and that normal parts of kidney look “mass-like” because these parts did not show atrophic change. Our question is what high-intensity sites on T2 mean. High-intensity signal on T2 usually means fluid. Is this case an artifact? Anyway, in this case, it was not easy to diagnose IgG4-RKD and to evaluate the distribution of IgG4-RKD only by radiological findings because his imaging examination did not show typical results in terms of previous reports. Advanced TIN probably modified the radiological findings.

We have revised the description on radiological findings and discussion through our manuscript.

2. “In the abstract, the authors state that the renal prognosis of IgG4-related kidney disease is good because of a slow progression of kidney failure. However, Tsubata et al (Tsubata K et al. Intern Med. 2010;49(15):1593-8) analyzed 16 reported cases and found that the time course of renal function was divided into two types, i.e., acute cases and chronic cases and renal failure progressed rapidly in a few months in a group of acute cases. Therefore, the description "a slow progression of kidney failure" is incorrect.”

Response: Thank you for the evidence of renal prognosis of IgG4-related kidney disease by Tsubata et al. They showed series of acute decrease of kidney function over a few months. We have deleted the description "a slow progression of kidney failure" in abstract and conclusions.

3. “The description "IgG4-positive lymphocyte infiltrate" in line 4 page 7 is incorrect. Please change the description to "IgG4-positive plasma cell infiltrate".

Response: Thank you very much for a reasonable comment. We have changed the description from "IgG4-positive lymphocyte infiltrate" to "IgG4-positive plasma cell infiltrate".