Author's response to reviews

Title: Gastrointestinal stromal tumor with nephrotic syndrome as a paraneoplastic syndrome: Report of a case

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Version: 5 Date: 11 January 2014

Author's response to reviews: see over
Dear Professor Kidd,

Enclosed, please find the revised version of our manuscript (1714873777111079) entitled “Gastrointestinal stromal tumor with nephrotic syndrome as a paraneoplastic syndrome: Report of a case” by K. Takane et al. for consideration for publication in JOURNAL OF MEDICAL CASE REPORTS. We have also included our point-by-point responses to the reviewers’ comments. We appreciate the thorough review of the original manuscript and in most cases agreed with the reviewers’ comments and have revised the manuscript accordingly. The revised passages are underlined in the text. We hope the revised manuscript is now suitable for publication in JOURNAL OF MEDICAL CASE REPORTS.

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Thank you for consideration.

Sincerely yours,

Yutaka Midorikawa
Author's response to reviews

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Author's response to reviews: see over
Object: MS: 17148737771111079 - Gastrointestinal stromal tumor with nephrotic syndrome as a paraneoplastic syndrome: Report of a case

Thank you for consideration of our manuscript for publication in your journal.
We have reviewed the above manuscript according to your reviewer’s comments.

Reviewer # 1 (Dr Jeffrey Kopp)

Major comments:

1. This case is instructive. I would like to know the most recent urine protein levels. It appears that no kidney biopsy was performed; this should be mentioned and the rationale.

   • In accordance with the reviewer’s comment, we added the most recent urinary protein level.

   “The patient remains well with no recurrence of the tumor or nephrotic syndrome (the recent urinary protein level: 1.19/dl) 2 years after surgery.”
   (page 5, line 3)

   • As indicated by the reviewer, we referred to the reason why no kidney biopsy was performed for our patient.

   “Laboratory examinations revealed hypoproteinemia (4.8g/dl; normal range, 6.5 to 8.0), hypoalbuminemia (2.2 g/dl; normal range, 3.8 to 5.3), and severe proteinuria (8.47 g/dl; normal range, 0 to 0.15), and the protein creatinine ratio was 14.3and amount of urine for 24 hours was 1200ml, clinically suggesting nephrotic syndrome. Therefore, the kidney biopsy was not carried out because it was for avoiding an invasive inspection.”
   (page 4, line 7 to11)
Minor comments:

1. **P5:** rephrase the sentence that begins “gastric cancer 25%” to indicate that these percentages of tumor-associated NS and not of gastric cancers, etc.

   - The sentence pointed out by the reviewer was rewritten as follows.

   “Gastric cancer, lung cancer, and malignant lymphoma are frequently associated with nephrotic syndrome of which rate are 25, 15 and 10%, respectively [8].

   (page 5, line 9 to 10)

2. **P6:** rephrase the sentence about tumor antigen reduction to make clear that this is speculation

   - As indicated by the reviewer, the sentence about tumor antigen reduction after surgery is just speculation and we deleted it.

3. **Figure 1:** it is difficult to appreciate what is stomach and what is liver, and to interpret the 4 lucencies, one accompanied by calcification. More text in the legend and arrows or other symbols would clarify this.

   - In order to clarify the gastric tumor, we indicated the tumor and stomach using arrow and arrow head.

   “A computed tomographic scan, showing a large tumor measuring 56 × 55 mm and accompanied by calcification. Arrow indicate the tumor and arrow head the stomach.”

   (page 10, line 4)

Reviewer #2 (Dr Preeti Chandra)

1. The proteinuria of 8.47 g/dl – what was the protein creatinine ratio and what was the 24 hour urine collection?

   - As indicated by the reviewer, we added the protein creatinine ratio 24 hour urine collection.
Laboratory examinations revealed hypoproteinemia (4.8g/dl; normal range, 6.5 to 8.0), hypoalbuminemia (2.2 g/dl; normal range, 3.8 to 5.3), and severe proteinuria (8.47 g/dl; normal range, 0 to 0.15), and the protein creatinine ratio was 14.3 and amount of urine for 24 hours was 1200ml, clinically suggesting nephrotic syndrome. Therefore, the kidney biopsy was not carried out because it was for avoiding an invasive inspection.

2. How long after tumor resection did the proteinuria start to resolve?

- As indicated by the reviewer, we referred to the period in which the proteinuria start to resolve.

“One week after operation, the serum albumin (3.3 g/dl) and urinary protein (1.71 g/dl) level remarkably improved after removal of the tumor.”

3. No renal biopsy was done to determine the histopathology. The diagnosis of paraneoplastic nephrotic syndrome and hence a paraneoplastic glomerulopathy should rely on three criteria.

- As suggested by the reviewer, the histological change after operation is impossible to diagnose PNS. In the present case, nephrotic syndrome was clinically define, which was improved after removal of the tumor. In addition, kidney biopsy is invasive and therefore, we avoided it.

“Laboratory examinations revealed hypoproteinemia (4.8g/dl; normal range, 6.5 to 8.0), hypoalbuminemia (2.2 g/dl; normal range, 3.8 to 5.3), and severe proteinuria (8.47 g/dl; normal range, 0 to 0.15), and the protein creatinine ratio was 14.3 and amount of urine for 24 hours was 1200ml, clinically suggesting nephrotic syndrome. Therefore, the kidney biopsy was not carried out because it was for avoiding an invasive inspection.”

4. More detail is needed to describe if the patient was taking concomitant medications for eg NSAIDS that can cause MCD that will resolve after stopping the NSAIDs or if this was a membranous nephropathy that resolved spontaneously irrespective of the tumor.
The patient did not take NSAIDs before operation because she did not suffer from fever or pain. We added the following sentence as indicated by the reviewer.

“She had no previous medical history and was not complaining of fever and therefore, she was not taking oral non-steroid anti-inflammatory drugs.”

(page 4, line 2 to 4)

5. The authors do not mention if any other agents were used to treat the tumor including tyrosine kinase inhibitors such as sunitinib— which have been associated with proteinuria themselves. Given that the nephrotic syndrome appears to have been diagnosed at the same time as the tumor itself, it does not appear that there were agents given prior to this, but a clarification will be useful in the discussion.

As indicated by the reviewer, tyrosine kinase inhibitors may cause the proteinuria. In the present case, such agents were not administered, and we referred to it in Discussion.

“On the other hand, clinical remission of nephrotic syndrome was obtained immediately after tumor removal. Considering that the patient did not take drugs perioperatively which causes nephrotic syndrome such as non-steroidal anti-inflammatory drugs or tyrosine kinase inhibitors, the nephrotic syndrome was a PNS associated with the GIST of the stomach.”

(page 5 line 16 to page 6 line 3)

6. Page 6-2nd line from the top—“In our patient, the number of antigens decreased by tumor excision, followed by histological normalization of glomeruli, thereby improving nephrotic syndrome.” Its unclear why the authors would write this statement— since there is no mention of any tumor antigens identified in the manuscript and no renal biopsy was done to confirm histological changes resolved with tumor resection.

As indicated by the reviewer, the sentence about tumor antigen after surgery is just speculation and deleted it.