April 8, 2013

Dear Editor,

Please find enclosed edited manuscript in Word format (file name: 2253-review.doc).

Title: Polyarteritis nodosa clinically mimicking nonocclusive mesenteric ischemia

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 The title has been modified according to the journal format.

3 Revision has been made according to the suggestions of the reviewers.

(1) Is the high number of authors justified considering the work is of a case report? Did all authors contribute significantly to the work?

Although many physicians participated in treating this patient, we made corrections of the coauthors to reduce the numbers according to their contributions.

(2) Initial CT and PET were taken from which body area? "Emphysema" suggests chest, but it is unclear. What were the authors looking for in findings?

Although torso CT and whole-body PET were taken for the screening of inflammatory, infectious, or tumorous lesions, abnormal finding was only the emphysema.

We corrected the sentences as follows,

Torso computed tomography (CT) revealed emphysema alone, and whole-body positron emission tomography (PET) yielded negative results.

(3) There are two interesting aspects of the case: MPO-ANCA positivity and the presentation as NOMI. The authors could discuss similar cases, if any.
Reference 14 describes a case with intestinal ischemia involvement as well, are there other similarities with this case that are worth discussing?

We could find only one case (Reference 14) which described positive MPO-ANCA and vasculitis in intestinal medium-sized arteries although their case was autopsy. In their article, the titer of MPO-ANCA was low, and was not correlated with the severity of PAN. These points were similar to our case, and we speculate the epitope and pathogenicity might be different from those of MPO-ANCA found in MPA.

We added the sentences as follows,

Tanaka et al.[14] described a case of PAN with MPO-ANCA and vasculitis in mesenteric medium-sized arteries, which was confirmed by autopsy. In their case, the titer of MPO-ANCA was low and was not correlated with the severity of PAN. These points were similar to our case, and we speculated that the epitope and pathogenicity may be different from those of MPO-ANCA found in MPA.

(4) Discussion on the ACR criteria for PAN is warranted. The patient clearly fullfilled the diagnostic criteria (Arthritis Rheum, 33 (1990), pp. 1088–1093).

This patient clearly fulfilled the American College of Rheumatology 1990 criteria for the classification of PAN.

We added the sentences as follows,

Although MPO-ANCA was also weakly positive in this case, this patient clearly fulfilled the American College of Rheumatology 1990 criteria for classification of PAN[19], the pathological findings were typical of PAN as shown in Figure 3, and vasculitis was absent in arterioles, capillaries, and venules.

(5) What management, and what implications, were given to the hypertension? Was it renal vascular involvement? Rhabdomyolisis? Glomerulonephritis?

We speculated the cause of hypertension was vasculitis probably renal vascular involvement. Although urinary tests showed 3+ occult blood and urinary sediments revealed low numbers of red blood cells, which indicated that he was also suffered from myoglobinuira, rhabdomyolisis was not considered to be severe enough to manifest hypertension. Because red blood cell casts were absent in urinary sediments, we considered he was not suffering from glomerulonephritis.
We treated hypertension using interavenous nicardipine.

We corrected the sentence as follows,

He received pulsed methylprednisolone at a dose of 1 g for 3 days followed with PSL at 60 mg/day because the underlying disease was considered to be vasculitis, and intravenous nicardipine for hypertension, which was considered to be caused by renal vascular involvement.

(6) Were pulses absent from an extremity, or other findings suggesting Takayasus? Rits et al (J Vasc Surg. 2010 Feb;51(2):392-400.e2) describe a series of mesenteric vasculitis involving 4 patients with PAN, but Takayasus was more frequent.

His pulses from extremities were present, and major aortic arteritis was not detected by torso CT and whole-body PET. So we convinced that he was not suffered from Takayasu arteritis.

(7) Other series (28 patients) found intestinal ischemia in 30% of cases of PAN (Am J Med. 2002 Apr 1;112(5):386-91.). These authors also developed a risk score, and found that nervous system, renal, and hypertensive alterations are common in patients with PAN and intestinal symptoms. I suggest the authors check these references, and if useful or relevant, consider integrating them into their discussion. See also (Clin Gastroenterol Hepatol. 2008 Sep;6(9):960-6.)

We integrated some sentences into discussion according to the reviewer's suggestion.

Although GI ischemia has been reported to occur at a rate of 13% – 31% in PAN patients[3, 5], the prevalence of PAN itself is very low, and clinical suspicion of vasculitis is sometimes difficult in cases showing intestinal necrosis.

Peripheral nervous system vasculitis, hypertension, cutaneous lesions, and myalgias were reported to be more common in PAN with than without GI involvement[5], and our patient also manifested most of these symptoms with the exception of cutaneous lesions.

(8) The authors state that glomerulonephritis was absent, but the patient has proteinuria, hematuria. Did they biopsy kidney as well? Did the patient develop renal failure at any point in his evolution? Was angiography considered at any point?

Although we wanted to perform kidney biopsy to clarify the renal involvement as reviewers pointed out, it was difficult considering the patient's condition. Because red blood cell casts were not detected, we considered this patient was not suffered from glomerulonephritis. His urinary testing was improved after the surgery, and he did not develop renal failure. We performed CT angiography, but we could not detect renal artery aneurysm.
We speculated that glomerulonephritis was absence in this case, but it was not proven histologically, so we want to correct the sentence as follows,

Although MPO-ANCA was also weakly positive in this case, this patient clearly fulfilled the American College of Rheumatology 1990 criteria for classification of PAN[19], the pathological findings were typical of PAN as shown in Figure 3, and vasculitis was absent in arterioles, capillaries, and venules.

(9) The authors could comment on the therapeutic options for patients similar as theirs after reviewing the literature. (steroids, cyclophosphamide, plasma exchange, etc.) Check reference 6.

We added following sentences into discussion.

The standard regimen for PAN, not related to hepatitis B virus infection, is based on a combination of corticosteroids (CS) and cyclophosphamide (CY)[20]. The addition of CY to CS particularly benefits patients presenting with factors associated with poor prognosis, such as GI involvement. Intermittent pulse-therapy may be as efficacious as oral CY for inducing remission, while generating fewer side effects. Treating PAN patients positive for factors associated with poor prognosis with 12 rather than 6 CY pulses significantly decreased the relapse rate and significantly increased the probability of event-free survival[20]. Plasma exchange can be prescribed for severe life-threatening PAN as combined rescue therapy, although trials have not proven its benefits when prescribed systematically for all patients with PAN[21]. In addition, the surgical management of patients with acute abdominal syndromes has also improved, and now includes more aggressive surgical management, bowel rest, parenteral nutrition, intensive care unit support, and better wound care[5].

(10) Table 1. The laboratory values on admission could be in the table, and any changes along the patients evolution could be then mentioned in the text. (Not 2 columns)

Considering another reviewer's suggestion (No.13), we corrected Table 1.

(11) Figure 2: The CT does not show the celiac trunk, and is not representative of the superior mesenteric artery. Are there CT-angiographic reconstructions? These would be interesting.

We replaced figures which showed the celiac trunk and superior mesenteric artery. We also added CT angiographic reconstruction, and figure legends.

(12) During surgery 2m of bowel were resected. How is the patient feeling now? Has the stoma in the meantime been closed again? Can the patient eat everything? Can he feed himself normally?

At present, the patient eats regular diet, and supplemental nutrition is not needed. Because his nutritional status has been improved and the dose of PSL is 10 mg/day, his stoma will be closed in April 2013.

We added following sentences.

As his nutritional status had improved because he became able to eat a regular diet without supplemental nutrition, his stoma was closed in April 2013.

Although small intestinal stoma, central venous catheter, subnutrition, and immunosuppressive therapy caused many life-threatening complications, close monitoring and appropriate treatment resulted in complete remission of PAN and eventual closure of his stoma.

(13) *Laboratory data (table 1): it is not very interesting to compare the laboratory findings between April and May 2012. In addition, the data pre and post surgery should be given. The authors report that the patient is now doing well and is in complete remission. The present laboratory data should be presented.*

Considering another reviewer's suggestion (No.10), we corrected Table 1.

3 References and typesetting were corrected

4We added some sentences to abstract because the word counts were under the required counts.

5.Some sentences were proofread.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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