

January 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 847-case report.docx).

**Title:** Behçet's disease complicated by multiple aseptic abscesses of liver and spleen

**Author:** Keisuke Maeshima, Koji Ishii, Megumi Inoue, Katsuro Himeno, Masataka Seike

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 847

**Reviewer:** 00070162

We deeply appreciate the concerns of the reviewer and recommendations for improving our presentation. Since we think that the reviewer's comments are important, we have intensively changed and modified the description in the manuscript.

The followings are a point-by-point reply to the critiques:

1) There are several grammatical and spelling errors in the current manuscript that need to be corrected:

- line 16: (has) have been described  
P.2, L19: "has" → "have"
- line 45: neutrophils "infiltration"  
P.3, L53: We added "infiltration".
- line 55: 20-yeras-old  
P.4, L61: "20-year-old" → "20-years-old"
- line 57 and 73: at age 16/ at age 19: it should be better "When he was sixteen years-old...or "at the age of 16"  
P.4, L63: "At age 16" → "At the age of 16"  
P.4, L77: "at age 19" → "at the age of 19"
- line 109: "as of": in February 2012  
P.5, L113: "as of" → "in"
- line 116: "AAs are a diagnosis of exclusion" The diagnosis of AAs is of exclusion on the....  
P.6, L121: "AAs are a diagnosis of exclusion" → "The diagnosis of AAs is of exclusion"
- line 137: Neutrophilic dermatoses are ..... ("is")  
P.6, L146: "is" → "are"
- line 150: A patient with Crohn's disease and associated AAs  
P.7, L161: "A patient with AAs associated with Crohn's disease" → "A patient with Crohn's disease and associated AAs"
- line 156: "in summary", in conclusion  
P.7, L166: "In summary" → "In conclusion"
- References: may the length of DOI should be reduced

- P.8, L177: “[PMID: 17505254 DOI: 10.1097/md.0b013e18064f9f3 00005792-200705000-00003 [pii]]” → “[PMID: 17505254 DOI: 10.1097/md.0b013e18064f9f3]”
- P.8, L179: “[PMID: 9008752 DOI: S024886639780848X [pii]]” → “[PMID: 9008752]”
- P.8, L187: “[PMID: 19279433 DOI: 10.1007/DCR.0b013e318199db60 00003453-200902000-00026 [pii]]” → “[PMID: 19279433 DOI: 10.1007/DCR.0b013e318199db60]”
- P.9, L212: “[PMID: 16301678 DOI: 175/11/7678 [pii]]” → “[PMID: 16301678]”
- P.9, L214: “[PMID: 16498453 DOI: nri1784 [pii] 10.1038/nri1784]” → “[PMID: 16498453 DOI: 10.1038/nri1784]”
- Figure 1: erythema nodosum on the.....

Following the other reviewer’s instruction, we deleted a picture of erythema nodosum for figure 1.

2) You say, in the decription of the case, that a colonoscopy with ileoscopy has been performed and this disclosed evidence of few small aphthous ulcers in the terminal ileum. The biopsies of the ileum, with the histological examination, have been performed to exclude a Crohn’s disease?

As pointed out by the reviewer, we added the following text to the Case Report section;

P.4, L94: “; pathological examination showed non-specific chronic inflammation without any evidences of Crohn’s disease such as noncaseating granuloma”

In addition, we corrected the following parts;

- P.4, L93: “a few small aphthous ulcers” → “a small aphthous ulcer”

3) In the case report you should use the same unit (normal value and pathological) of measures for WBC count and Hb ( mL or  $\mu$ L).

We corrected the following parts;

- P.4, L84: “13,400/mL” → “13,400/ $\mu$ L”
- P.4, L85: “ $57.1 \times 10^4$ /mL” → “ $57.1 \times 10^4$ / $\mu$ L”
- P.4, L88: “583 IU/L” → “583 U/L”
- P.4, L89: “123 IU/L” → “123 U/L”

## Reviewer: 01436310

We deeply appreciate the concerns of the reviewer and recommendations for improving our presentation. Since we think that the reviewer’s comments are important, we have intensively changed and modified the description in the manuscript.

The followings are a point-by-point reply to the critiques:

1) Although the patient fulfills the Japanese criteria for Behçet disease, he doesn’t meet the International Study Group for Behçet’s Disease criteria. Differential diagnosis must be clearly discussed such inflammatory bowel diseases (IBD) (aphthous ulcers in the terminal ileum, oral ulcers and pericarditis that are possible features of IBD). Particularly in Japanese patients, there is an overlapping in Behçet disease and Sweet syndrome as discussed page 7 but these differential diagnoses should appear in a separate section.

As pointed out by the other reviewer, we added the following text to the Case Report section;

P.4, L94: “; pathological examination showed non-specific chronic inflammation without any evidences of Crohn’s disease such as noncaseating granuloma”

In addition, we corrected the following parts;

- P.4, L93: “a few small aphthous ulcers” → “a small aphthous ulcer”

P.6, L137: We separated a section about differential diagnosis.

P.6, L137: We added “The differential diagnosis of Crohn’s disease vs. BD can be difficult. Although ulcerative lesions at the ileocecal area are common both in these diseases, we diagnosed the patient as having intestinal BD because of a lack of factors suggestive of Crohn’s disease. Thus, the number of his ulcerative lesion was only one, its shape was not longitudinal, and histopathological examination showed no granulomatous lesion.”.

P.6, L141: We added “also”.

P.6, L142: We added “, because some overlapping manifestations exist between BD and Sweet’s disease”.

P.6, L149: We added “Extracutaneous neutrophilic infiltrates are observed in all forms of neutrophilic dermatoses, but they predominate in Sweet’s syndrome<sup>[11]</sup>. Sweet’s disease in association with BD has been reported and there seems to be something in common for the pathogenesis of BD and Sweet’s disease<sup>[12]</sup>.”.

P.8, L200: We added “11 Vignon-Pennamen MD. The extracutaneous involvement in the neutrophilic dermatoses. *Clin Dermatol* 2000; **18**(3): 339-347 [PMID: 10856666]”.

P.8, L202: We added “12 Wu F, Luo X, Yuan G. Sweet’s syndrome representing a flare of Behcet’s disease. *Clin Exp Rheumatol* 2009; **27**(2 Suppl 53): S88-90 [PMID: 19796541]”.

In the abstract, the authors argue that AA associated with Behçet disease is extremely rare but in the introduction, the sentence page 2 “AAs associated with BD has never been reported” is contradictory.

- P.3, L57: “AAs associated with BD have never been reported to date” → “AAs associated with BD are extremely rare”
- P.3, L57: We deleted “first”.
- P.6, L135: We added “unfailing”.

Abstract : Severe inflammatory cell infiltration... was instead of were

- P.2, L25: “were” → “was”

Why low dosage of colchicine has been used (only ? mg per day)?

Since colchicine was ineffective, we escalated the dose to 1.5mg/day. However, side effect such as diarrhea occurred and the patient wished to reduce the dose. Therefore, we continued a daily dose of 0.5 mg of colchicine, but the effect is still not obvious. Therefore, we consider to withdraw the use of colchicine, now.

- P.4, L79: “0.5mg/day” → “maximum dose being 1.5mg/day”

Figure 1 showing erythema nodosum should be deleted as it provides no further information. Are the authors sure that these lesions did not represent cutaneous aseptic abscesses?

We deleted a picture of erythema nodosum for figure 1. We are convinced that these lesions did not represent cutaneous aseptic abscesses.

Page 5, units of measure must be unified.

- P.4, L84: “13,400/mL” → “13,400/μL”
- P.4, L85: “57.1×10<sup>4</sup>/mL” → “57.1×10<sup>4</sup>/μL”
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It would be interesting to discuss the interest of a PET scan in August 2010 (page 6) because it has been demonstrated to display early AA lesions.

“obvious abnormality(P.5, L109)” means that he did not have fever, abdominal pain, or other signs of local or

systemic infection. We did not perform even abdominal US or CT at the time. Indeed, FDG-PET would reveal early phase of AAs, however it seems to be inappropriate that we discuss about PET here.

Page 6, what was planned to taper steroids below 15 mg?

Actually, we tried to taper the dose of prednisone several times, however elevated CRP, which strongly suggests the relapse of AAs, was observed each time. Therefore, we must needs continue 15mg/day of prednisone. But now, we consider the introduction of TNF inhibitor in anticipation of steroid-sparing effect.

Discussion: the spectrum of AA should be discussed as it overlaps with other conditions as it was pointed out in the Medicine review in 2007. Sweet syndrome and Behcet disease share numerous features in Japan population.

P.5, L119: We added “Most patients with AAs had some underlying disease, and it was speculated that AAs belong to the spectrum of autoinflammatory multifactorial disorders<sup>[1]</sup>.”.

P.5, L117: We added “We present a patient with BD who developed AAs in spleen and liver.”.

## Others

We also corrected the part of correspondence;

- P.1, L10: “Keisuke Maeshima, MD, PhD” → “Koji Ishii, MD, PhD”
- P.1, L15: “maeshima@oita-u.ac.jp” → “kois@oita-u.ac.jp”

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

Sincerely yours,

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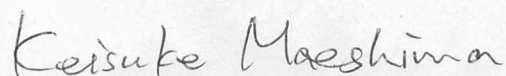
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