Author’s response to reviews

Title: Mesenteric inflammatory veno-occlusive disease occurring during the course of ulcerative colitis: A case report.

Authors:  
Yosuke Yamada (yosuke.h.smile@gmail.com)  
Ken Sugimoto (sugimken@hama-med.ac.jp)  
Yashiro Yoshizawa (yashiro1224@sis.seirei.or.jp)  
Yoshifumi Arai (araiyoshi@sis.seirei.or.jp)  
Yoshiro Otsuki (otsuki@sis.seirei.or.jp)  
Tomio Arai (arai@tmig.or.jp)  
Yasuyuki Kobayashi (cobayasu@sis.seirei.or.jp)  
Yoshihiko Sato (cbf01951@nifty.com)  
Yoshisuke Hosoda (yhosoda@sis.seirei.or.jp)

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Author’s response to reviews:

December 15, 2017

Subject: Revised Manuscript (BMGE-D-17-00481R1), “Mesenteric inflammatory veno-occlusive disease occurring during the course of ulcerative colitis: A case report.”

Dear Siew C Ng:

We are grateful for the opportunity to revise our manuscript (BMGE-D-17-00481R1) and for the helpful suggestions and comments provided by the reviewers. We have addressed the reviewers’ concerns, comments, and questions, and have presented our detailed responses below in a point-by-point manner.
We hope that these revisions strengthen our manuscript and make it suitable for publication. We have uploaded marked and unmarked copies of the manuscript.

RESPONSE TO REVIEWER #1 (Dr. Heyson Chan):

We appreciate your insightful comments, which have helped us significantly improve the manuscript.

1. Please quote the references to support the statements "MIVOD is mostly resistant to medical treatment, as anticoagulants and immunoregulatory drugs have proven ineffective for patients with MIVOD" and "In most cases, surgical resection of the involved bowel is required and prognosis is typically excellent"

Authors’ response: As you suggested, we added two references, i.e., ref.7 (ref.11 in the prior version of this manuscript) and ref.8 (ref.15 in the prior version), to support the following: "MIVOD is mostly resistant to medical treatment, as anticoagulants and immunoregulatory drugs have proven ineffective for patients with MIVOD” and "In most cases, surgical resection of the involved bowel is required and prognosis is typically excellent" (Background section, line 10-11, page 3, in the unmarked new version of this manuscript). We also updated the reference numbers.

2. There is inconsistency in the age of the patient in the abstract and the case presentation. Does the authors mean that the patient was 29 years old when he first presented in the case presentation section? The authors should consider specifying that this sentence refer to the initial presentation 3 years ago rather than this episode.

Authors’ response: As you suggested, we changed, “A 29-year-old man initially visited our hospital with the chief complaint of bloody stool.” to “A 32-year-old man initially visited our hospital with the chief complaint of bloody stool at the age of 29.” (Case presentation section, line 16-17, page 3).

3. It was stated that the patient was diagnosed with moderate UC and his symptoms was "relatively" controlled with oral 5ASA, did the patient achieved clinical remission or still having clinical symptoms before the flare? Was there any endoscopic assessment?

Authors’ response: Prior to the relapse of UC in this patient, blood tests showed no inflammation and no abdominal symptoms were observed except for mild loose stools. Accordingly, we added this information in the new Fig. 5. Since the patient refused the procedure, endoscopy was not performed before relapse.
4. Consider a new paragraph to describe the flare at age 32.

Authors’ response: As you suggested, we described his flare at age 32 in a new paragraph.

5. Consider elaborating the symptoms experienced by the patient during the possible flare. Was there any PR bleeding? Did the patient fit the definition of severe flare by Truelove criteria?

Authors’ response: He had rectal bleeding at relapse and met the criteria for a severe flare in the Truelove and Witts severity index. Accordingly, we added the following text (page 3, line 23 to 25, in the unmarked new version of this manuscript).

“He had rectal bleeding and his disease activity was severe according to the Truelove and Witts severity index.”

6. In the sentence, "Basal plasmacytosis and eosinophil infiltration were unremarkable and there was no typical "owl eye" inclusion indicating CMV infection (Fig.3a)." Do the authors mean Fig 3b instead?

Authors’ response: “Fig. 3a” was our mistake. We changed this to “Fig. 3b” (Case presentation section, line 13, page 4).

7. What was done to exclude other possible differential diagnosis e.g. Buerger's disease, Behçet's disease, rheumatoid arthritis and systemic lupus erythematosus?

Authors’ response: Based on clinical findings, Buerger's disease, Behçet's disease, rheumatoid arthritis, and systemic lupus erythematosus were excluded, and this was added in the text. (Case presentation section, line 13-14, page 4).

8. Please include the latest medication of the patient after surgery.

Authors’ response: As you suggested, we reported the latest medication used in this patient after surgery (oral 5-aminosalicylic acid). Accordingly, the text in the manuscript has been revised (Case presentation section, line 10, page 5).
9. It was mentioned that CMV was excluded at the presentation. However, in the post-operative period, the patient was complicated with CMV infection. How was the post-operative CMV infection diagnosed and how was it being treated?

Authors’ response: Given the positive finding of CMV-C7HRP in his blood during management in the postoperative ICU, administration of ganciclovir was performed and we confirmed a negative result for CMV-C7HRP 14 days after administration of ganciclovir. Accordingly, the text in the manuscript has been revised (Case presentation section, line 6-8, page 5).

10. It was quoted that "Previous reports indicate three cases of suspected MIVOD with UC. All of these cases had left-side colonic lesions and failed to respond to the appropriate treatment for UC, leading to required colectomy one to two weeks after the initial treatment” with reference 11 and 14. In the two cases of reference 11, the first patient was actually initially thought to be UC but was diagnosed with protein S deficiency - so this patient is actually NOT having ulcerative colitis. The second patient was actually having Clostridium difficile infection and was never diagnosed UC. The authors may wish to go over the paper in detail and clarify if the statement can be supported by the reference they have quoted. The case presented in reference 14 also appeared not to be related to UC - please check.

Authors’ response: Thank you for noting the important points in references 11 and 15 in the Discussion section. We carefully checked these references and determined that these cases did not actually have ulcerative colitis. Therefore, we deleted the following from the Discussion section: "Previous reports indicate three cases of suspected MIVOD with UC. All of these cases had left-side colonic lesions and failed to respond to the appropriate treatment for UC, leading to required colectomy one to two weeks after the initial treatment."

11. This case of MIVOD occurred in the course of UC and MIVOD was confirmed at day 35 of UC flare by the histological specimen from the colectomy. The patient did not have any imaging evidence of MIVOD at the initial presentation of the suspected flare up of UC. With the 35-day delay in the diagnosis of MIVOD and the initial imaging, it is hard to conclude whether the imaging failed to pick up the MIVOD or whether MIVOD occurred as a consequence of the hypercoagulable status from UC flare. The author should address this in their discussion.

Authors’ response: Thank you for your suggestion. As we stated on page 5, line 25, it is very difficult to diagnose MIVOD with endoscopic findings alone because UC and MIVOD have similar endoscopic findings, but there are no endoscopic findings specific to MIVOD. In addition, since the postoperative specimen revealed that the surface mucosal structure of the colon at the site where phlebitis and venous thrombus were present was relatively maintained, it
seemed unlikely that secondary thrombus was formed by exacerbation of UC. In line with your suggestion, this point has been discussed in further detail in the Discussion section. We added the following text (page 6, line 12 to 17).

“Because UC and MIVOD have similar endoscopic findings and there are no endoscopic findings specific to MIVOD, it is very difficult to diagnose MIVOD with endoscopic findings alone. In addition, since the postoperative specimen revealed that the surface mucosal structure of the colon at the site where phlebitis and venous thrombus existed was relatively maintained, it seemed unlikely that secondary thrombus was formed by exacerbation of UC.”

12. The authors may wish to add a timeline to illustrate the event sequence.

Authors’ response: As you suggested, we added a timeline to illustrate the event sequence as Fig. 5. Accordingly, the following text was added (Case presentation section, line 11, page 5).

“The clinical course of this patient is shown in Fig. 5.”

RESPONSE TO REVIEWER #2 (Dr. Satimai Aniwan):

We appreciate your insightful comments, which have helped us significantly improve the manuscript.

1. What is smoking status of this patient?

Authors’ response: He is a never smoker. We added this to the background on this patient in a new Fig. 5.

2. Does patient have any other medical diseases?

Authors’ response: He did not have any other medical diseases. We added this to the background on this patient in a new Fig. 5.

3. Please provide detail of duration/onset of abdominal pain before admission?
Authors’ response: As you suggested, we added details of the duration/onset of abdominal pain in a new Fig. 5.

4. Even though symptoms of UC are hardly differentiated from symptoms of MIVOD, could the authors provide comment on either MIVOD could explain the all clinical course of the patient since admission or MIVOD are the complication of severe refractory UC?

Authors’ response: Thank you for your suggestion. As we stated on page 5, line 25, because UC and MIVOD have similar endoscopic findings and there are no endoscopic findings specific to MIVOD, it is very difficult to diagnose MIVOD using endoscopic findings alone. In addition, since the postoperative specimen revealed that the mucosal surface structure of the colon at the site where phlebitis and venous thrombus existed was relatively maintained, it seemed unlikely that secondary thrombus was formed by exacerbation of UC. In line with your suggestion, this point has been discussed in further detail in the Discussion section. We added the following text (page 6, line 12 to 17).

“Because UC and MIVOD have similar endoscopic findings and there are no endoscopic findings specific to MIVOD, it is very difficult to diagnose MIVOD using endoscopic findings alone. In addition, since the postoperative specimen revealed that the surface mucosal structure of the colon at the site where phlebitis and venous thrombus existed was relatively maintained, it seemed unlikely that secondary thrombus was formed by exacerbation of UC.”

5. In the case presentation part, please describe mesenteric vessels on the CT-finding?

Authors’ response: As you suggested, we stated that there was no abnormality in the mesenteric vessels in the Case presentation section. Accordingly, the text in the manuscript has been revised (Case presentation section, line 7-8, page 4).

6. Any laboratory about hypercoagulability status is tested?

Authors’ response: As you suggested, we added the laboratory data showing hypercoagulability status in a new Fig. 5.

7. "consent of the surgery could not be obtained" please clarify. Is that the patient refused surgery or unconscious?
Authors’ response: Thank you very much for your suggestion. He strongly refused surgery, and consent was not obtained. Accordingly, the text in the manuscript has been revised (Case presentation section, line 20, page 4).

We hope that these revisions meet the approval of the reviewers and the editorial board and that our case report will be considered for publication in BMC gastroenterology.

Yours sincerely,

Ken Sugimoto, MD, PhD
(On behalf of authors)