

Dear Editor,

Thank you for your decision letter and advice on our manuscript (Manuscript NO: 89569) entitled “Link between mutations in *ACVRL1* and *PLA2G4A* genes and chronic intestinal ulcers: A case report and literature review”. We also appreciate the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are highlighted with yellow color in the revised manuscript. In addition, our point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Inc.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

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## Round 1

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Major revision

### **Specific Comments to Authors:**

1. The title does not mention the use of a new intervention

**Response:** We concur that treatment with Kangfuxin liquid is an important highlight of this case. However, due to the word limit for the title, we could not include this detail within the title.

2. With regard to the surgical procedure 7 yrs back - what was the exact site / size of the perforation? What was the procedure done?

**Response:** Since the patient was previously seen at another hospital, this part of the data is missing. Colonoscopy revealed that the anastomosis site between the ascending colon and the ileum was present 55 cm from the anus, with a missing ileocecal valve (60-70 cm away from the anus). It is speculated that the intestinal perforation at that time may have been located at the ileocecal region.

3. Were any bloods done in the line of IBD - Antinuclear abs, etc?

**Response:** These details of the blood work have been added to the manuscript (Page 9, Paragraph 2).

4. How was IBD ruled out? Why was Azathioprine considered in the background of 'undiagnosed' IBD?

**Response:** The patient had no clear-cut cause for chronic intestinal bleeding and intestinal perforation. The main affected areas were the ileum and ascending colon,

with ulcer formation, and other common causes of intestinal ulcer formation were ruled out, so the preliminary diagnosis was IBD. The patient received treatment with mercaptopurine at another hospital, but it was not effective. Considering these observations, the patient's young age at symptom onset, and lack of typical UC or CD manifestations, we thought it necessary to investigate genetic factors involved in the occurrence of chronic intestinal ulcers. Genetic testing of the patient's whole exome revealed mutations in the *ACVRL1* and *PLA2G4A* genes. *ACVRL1* and *PLA2G4A* are involved in angiogenesis and coagulation, respectively. The patient received treatment with oral Kangfuxin liquid, which was administered to promote healing of the intestinal mucosa. With this treatment, the patient's clinical symptoms were relieved. Thus, we ruled out IBD.

5. Were other causes for chronic ulcers such as immune disorders / Tuberculosis considered?

Response: We have revised the manuscript to include information relevant to exclude immune disorders/tuberculosis.

6. On what basis was the new oral medication (Kangfuxin liquid) used?

Response: The Kangfuxin liquid, which has a wound repair effect, has been extensively used in clinical practice in China for over 20 years. A substantial amount of clinical research data has been accumulated regarding the use of this medication, providing solid evidence of its effectiveness<sup>[41]</sup>. It has also been reported in the literature that the use of Kangfuxin liquid plus proton-pump inhibitor in the treatment of peptic ulcers significantly enhanced the healing rate and overall response rate of ulcers, alleviated the clinical symptoms of peptic ulcers, and reduced the recurrence of peptic ulcers<sup>[42]</sup>.

7. Any randomised trials are available in humans regarding the use of the new medication?

Response: Kangfuxin liquid, which has been approved by the China Food and Drug Administration, represents traditional Chinese medicine starting with "Z" (Z51021834; Page 24, Paragraph 2). It has undoubtedly undergone rigorous human trials and has been proven to be safe and effective.

8. What were the other medications used in this pt ("Yunnan Baiyao for hemostasis")?

Response: Basal medical treatment included omeprazole to suppress gastric acid production and Yunnan Baiyao to prevent bleeding, combined with azathioprine to regulate immunity.

9. What is the dosage / duration of administration of Kangfuxin liquid? How long is it planned to be given?

Response: Kangfuxin liquid was administered at a dose of 10 ml three times daily to promote intestinal repair. The course of treatment was 4 weeks.

10. What are the study limitations?

Response: There are a few limitations of this report. First, the link between mutations in the *ACVRL1* and *PLA2G4A* genes and chronic intestinal ulcers needs to be further verified via histopathological studies and in vivo animal experiments. Second, the patient's parents did not undergo whole-exome sequencing and colonoscopy examinations. Finally, the therapeutic effect of Kangfuxin liquid in chronic intensive ulcers and bleeding needs further verification in a more cases.

#### **4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH**

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other

related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Response: The manuscript has been revised for spelling, grammar, wording, and syntax, and further proofread by two native English editors from Madjaden, a publication service company. We hope that this manuscript reaches the quality for publishing in your journal.

**Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.**

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

## **5 ABBREVIATIONS**

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

**(1) Title:** Abbreviations are not permitted. Please spell out any abbreviation in the title.

**(2) Running title:** Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

**(3) Abstract:** Abbreviations must be defined upon first appearance in the Abstract.

Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

**(4) Key Words:** Abbreviations must be defined upon first appearance in the Key Words.

**(5) Core Tip:** Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

**(6) Main Text:** Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

**(7) Article Highlights:** Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (*H. pylori*)

**(8) Figures:** Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

**(9) Tables:** Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

## **6 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### ***(1) Science editor:***

The manuscript has been peer-reviewed, and it is ready for the first decision.

**Response:** Thank you for your comments.

### ***(2) Company editor-in-chief:***

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally

accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response: Thank you for the suggestion. We have prepared our manuscript accordingly.

## Round 2

Dear Dr. Yan,

Thank you for your decision letter and advice on our manuscript (Manuscript NO: 89569) entitled “**Link between mutations in *ACVRL1* and *PLA2G4A* genes and chronic intestinal ulcers: A case report and literature review.**” We appreciate the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated by red font in the revised manuscript. In addition, our point-by-point responses to the comments are listed below this letter.

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With best wishes,

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First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

### **1. Please further revise the manuscript according to the comments second-round review.**

"1. "Laparotomy performed for exploration revealed the presence of intestinal perforation, and repair of the perforation was performed" - Which part of the small bowel / size of perforation?

**Response:** We were able to obtain the surgical record for the operation. The report indicated that laparotomy performed for exploration revealed diffuse peritonitis, acute gangrenous appendicitis with perforation, adhesive intestinal obstruction, and pelvic



abscess. The perforation occurred as a distal rupture of the appendix, with adhesions to the right iliac fossa. The size of the perforation was approximately  $0.7 \times 0.7$  cm.

2. "Treatment with azathioprine was administered, but it proved to be ineffective" - What was the dose / protocol? Why was it started and why was it found ineffective?

**Response:** The patient had a history of acute gangrenous appendicitis with perforation and has previously undergone appendectomy, intestinal adhesiolysis, and pelvic abscess resection. One year after the operation, the patient had recurring abdominal pain, diarrhea, and bloody stools. The symptoms of bloody stools were more prominent. Colonoscopy at this time revealed scattered ulcers in the ileum and ascending colon, which were suggestive of inflammatory bowel disease (IBD). On the basis of the patient's clinical features of recurrent abdominal pain, diarrhea, and bloody stools as well as the colonoscopy and pathological findings, the clinical diagnosis was established as IBD without the typical features of Crohn's disease or ulcerative colitis. Oral treatment with mesalazine was administered at a local hospital, at a dose of 2 tablets four times a day for a total of 6 weeks. However, there was no improvement in the symptoms of rectal bleeding. Subsequently, oral treatment with azathioprine was added, at a dose of 50 mg once a day for a total of 2 months. Even with this treatment, the symptoms of rectal bleeding did not improve. The Mayo score was 8 points both before and after medication (with an increase of 2-3 times per day compared to normal bowel movements, mixed blood in the stool within less than half of the time, ulcer formation detected by endoscopy, and moderate condition). Considering its ineffectiveness, azathioprine treatment was discontinued.

3. "No abnormal findings were obtained in laboratory tests for antineutrophil cytoplasmic antibody, antinuclear antibodies" - on what basis was the IBD diagnosis made?

**Response:** The diagnosis of IBD was made on the basis of the following signs and symptoms:

- (1) The primary symptom was recurring intestinal bleeding.
- (2) Colonoscopy revealed scattered erosion and ulcers in the ileum and colon.

(3) Pathological examination indicated non-specific inflammatory changes in the ileum and colon.

(4) Other common causes of infectious enteritis and ulcers caused by medication were ruled out.

4. "revealed that the anastomosis site between the ascending colon and the ileum was visible 55 cm from the anus, with a missing ileocecal valve (60-70 cm away from the anus)"- when was resection / anastomosis done?

**Response:** The resection was done on June 2, 2015, that is, when the patient was 15 years old.

5. The ref cited for usage of Kangfuxin [Int Wound J. 2023 Sep;20(7):2855-2868] describes the usage of the same as a topical and not as oral preparation ["The conclusion is that the combination of KFX and basic wound care is effective in increasing the total clinical effectiveness and shortening the complete healing time of pressure ulcers."]"

**Response:** We have added the references for treatment with oral Kangfuxin liquid (PMID: 31662770, 33592844).

**Answer to reviewers:** Please provide point to point answer to all reviewers. Authors should revise their article according to the reviewers' comments/suggestions and provide point-by-point responses to each in a letter that is to accompany their resubmission.

**2. Please provide the informed consent of surgical treatment.**

**Response:** We have provided the informed consent form for surgical treatment.