Dear Editor of World Journal of Clinical Cases

We would like to thank editors of World Journal of Clinical Cases and unknown reviewers of our manuscript for carefully reading our manuscript and providing comments. We have addressed the concerns of the respected editor and reviewers as follows. In addition, we have revised the manuscript according to *Guidelines for writing and formatting high quality Case Reports* and *Guidelines and Requirements for Manuscript Revision: Case Report*.

It is worth mentioning that in the revised manuscript, the updated text appears in blue colour.

Kind Regards

Hongguo Zhao
MD
Department of Hematology,
The Affiliated Hospital of Qingdao University,
Qingdao, Shandong Province, China
E-mail: zhaohongguo6201@163.com

Reviewer's Comment: However, several questions need to answered before we draw the conclusion that gut inflammation was responsible for aplastic anemia. More than the gut inflammation, recurrent gut infections due to immunocompromised state of the patient most likely appears to be the cause of favorable response to MG or PR regimen.

The persistent refractoriness to various drugs that are well-known to be effective in the treatment of AA and the rapid recovery of autologous hematopoiesis following MG treatment strongly indicate the pathogenic association between chronic gut inflammation and AA. Chronic gut inflammation may be caused either by chronic gut infections or by dysbiotic gut microbiota, all of which may follow an acute gut infection. We think the persistently aberrant immune responses in AA are most likely to be sustained by the chronic gut inflammation rather than recurrent gut infections, because of the following reasons: (1) this patient had displayed a seven-year of serious suppression of autologous hematopoiesis and durative resistance to various drugs, and only after MG treatment had he gained an excellent hematological response, meaning that the gut inflammation had an existence at least for more than seven years; (2) he had undergone several episodes of recurrence within the one-year of treatment, with each recurrence occurring 7-8 weeks from the gastrointestinal inflammation eliminating preparations, meaning that this is an persistent pathology instead of reinfections; (3) the effect of acute infections (except for overwhelming acute infections with the overwhelming release of pro-inflammatory mediators) promote the proliferation and differentiation of hematopoietic stem/progenitor cells with skewing towards myeloid commitment, and the HSPCs exhaustion in AA indicates the presence of chronic inflammation; (4) this patient presented with moderate GI symptoms rather than acute onset of serious GI symptoms; (5) host immune system would rapidly return to the immune homeostasis after the resolution of pathogens in acute infections. The seven years of persistent bone marrow suppression was the result of actively chronic gut inflammation rather than recurrent gut infections. Immunocompromised state in this patient may be the result of the actively chronic gut inflammation and the serious suppression of bone marrow hematopoiesis, and would be corrected after recovery of autologous hematopoiesis unless the existence of inherited defects in innate or adapter immune responses. Studies have showed that defects in innate or adapter immune responses are closely associated with the development of inflammatory bowel diseases and other autoimmune diseases, with the better examples of ulcerative colitis and celiac disease. The actively chronic inflammation in the intestines may be better called as chronic gut inflammation, as it may be caused either by pathogenic invaders, altered gut microbiota or other environmental exposures (Reflected in page 13, line 2 to page 14, line 5).

1. Title needs to be modified as ‘manipulating gut inflammation’ does not appear to be an appropriate term?

We think the title may be better revised as ***Excellent response of severe aplastic anemia by treating gut Inflammation: Case report*** , adding a running title as ***pathogenic association and direct evidence***. (Reflected in the title of our manuscript)

2. Were any abdominal imaging studies such as ultrasound or CT performed as the patient had recurrent abdominal cramps with multiple polyps in colon and rectum?

We are sorry the imaging examination had not been performed in the one year of treatment.

3. Was upper gastrointestinal endoscopy performed?

We are sorry the upper gastrointestinal endoscopy had not been performed.

4. What was the type of the colorectal polyp: hyperplastic, hamartomatous or inflammatory or polyps? The described microscopic findings do not fit in to any of these polyps.

After consulting the gastroenterologist, the congested and swollen mucous membranes, the absence of vascular lakes and multiple polypi on endoscopic examination are the features of gut mucous inflammation. After consulting the pathologists, the structurally integrated enlarged lymphoid follicles and the infiltration of large amount of lymphocytes and plasma cells on pathological examination are in accordance with inflammatory proliferation. (Reflected in page11, line 10-18).

5. How does enlarged lymphoid follicles confirm gut inflammation. This can be normal finding.

Seen in item 4.

6. Was microbiota analysis done to understand the microbial flora of this patient and the changes in it? Was stool examination performed?

We are sorry the microbiota analysis was not done because this laboratory test is unable to be performed in our hospital. The stool examination was not recorded in his medical record.

7. Was aminoglycosides used intravenously before starting MG regimen orally?

Aminoglycosides had not been used intravenously before starting MG regimen orally. (Reflected in page page 9, line30 to page 10, line 3)

8. Provide appropriate references supporting the use of MG or PR regimen for the treatment of gut infections as mentioned in the Discussion.

MG regimen was originally designed to treat serious gut infections after intensive chemotherapies in patients with hematopoietic malignancies in our clinical practices, with an attempt to reduce the amount of bacteria and their metabolites so as to at utmost to reduce the absorption of endotoxins from intestinal lumen into blood circulation. This regimen has not been documented in articles. The use of mannitol and polyethylene to induce osmotic diarrhea and colon cleansing was suggested and learned from the gastroenterologists who use these drugs to clear the contents of gastrointestines before performing endoscopic examination (Reflected in the references No. 9). Gentamycin is a poorly absorbable and broad-spectrum antibiotic and has being widely used to treat various infections (Reflected in the references No. 8), and oral administration of gentamycin to treat gut infection had been widely used in our clinical practice. Rifaximin has showed to be able to modify the composition of gut microbiome which suggests the use in the treatment of autoimmune diseases and has been used to prevent GVHD after allo-HSCT. (Reflected in the references No. 53). Rifampicin may be better than rifaximin since apart from the eubiotic effect, absorbed rifampicin could serve as a mTOR inhibitor to breakdown the vicious circle induced by the activation of mTOR signing pathway (Reflected in the references No. 54 to No. 56 and page 18, line 2-13). Articles related to rifamycin in the treatment of autoimmune diseases are added to the references.

9. Mention previous studies or case reports/series where MG or PR or any other similar regimen was used to treat autoimmune diseases.

We have added some previous studies about the modulation of gut microbiota to treat autoimmune diseases. However this drugs have not been put into practice in the treatment of autoimmune diseases (Reflected in the references No. 52 to No. 56 and page18, line 3-15)