Re: Manuscript (ID-71706) entitled “Gastrointestinal amyloidosis in a patient with Smoldering Multiple Myeloma: A case report and literature review”

Dear Editorial Office,

Thank you very much for your letter and advice on our manuscript (ID-71706) entitled “Gastrointestinal amyloidosis in a patient with Smoldering Multiple Myeloma: A case report and literature review”. We also thank the reviewers for the constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter. If you have any questions, please feel free to contact us.

We hope that the revision is acceptable for publication in your journal, and we look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Ailing Liu

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

Replies to Reviewer #1:

The authors present a relatively rare case which is interesting for the readership of the journal. The article is well written and concise. Few specific comments are as follows:

1. The authors need to define the methodology of their literature search including the time period and search channels utilized.

Response: Thank you for raising this critical issue. The sentence “A comprehensive literature search was conducted with publication dates from January 1, 1990, to

August 31, 2021" was added in the revision.

2. There is another report from L. A. T. M. Liyanaarachchi et al (https://jpgim.sljol.info/articles/abstract/10.4038/jpgim.8141/) that should be mentioned.

Response: Thank you very much. The report is mentioned in the revision.

3. A table should be included to compare the study findings with those of the literature review to present comprehensively

Response: Thank you. A table has been added in the revised manuscript (Table 2).

Replies to Reviewer #2:

Ailing Liu and colleagues present a case report and literature review about gastrointestinal amyloidosis in a patient with smoldering multiple myeloma. The topic has particularity and novelty. This case highlights that high index of suspicion is required to diagnose gastrointestinal AL. For the most part the article is clearly written but there are several important issues that need clarification.

1. The patient was finally diagnosed with SMM coexisting with AL. Was AL caused by MM? The article was not described in detail.

Response: Thank you for raising this critical issue. In our case, AL was caused by SMM. AL is the most common form of systemic amyloidosis, accounting for approximately 70% of all cases. The monoclonal light chain (κ or λ) originates from the abnormal proliferation of bone marrow plasma cells. Multiple myeloma (MM) is a hematologic malignancy characterized by uncontrolled proliferation of monoclonal plasma cells in the bone marrow. AL can be primary amyloidosis or secondary to myeloma. Therefore, the patient was finally diagnosed with AL secondary to SMM. This has been added in the revision.

2. The author emphasized that the patient had no hypercalcemia, renal dysfunction, anemia or bone lesions. But laboratory investigations revealed anemia. It is a

contradiction.

Response: Thank you for raising this critical issue. Our patient had anemia and occult blood in stools. However, anemia improved once the gastrointestinal bleeding stopped. Therefore, the cause of anemia in the present case was gastrointestinal bleeding rather than bone marrow failure due to MM. Hence, the patient had no CRAB criteria.

3. How long did the patient remain in outpatient treatment after discharge? It was not mentioned whether the patient had been on maintenance therapy.

Response:Thank you for this question. The patient remained in outpatient treatment after discharge. She received outpatient chemotherapy every month for about 5 years.

4. When was the specific onset of the patient? It was not mentioned in the full text. And what was the recovery status of the patient after the first treatment? Only symptoms were mentioned, no changes in laboratory markers or bone marrow recovery. What was the trend of urinary kappa chain and lambda chain?

Response:Thank you for your question. The patient was admitted to our hospital in November 2016 due to pedal edema for four months, abdominal distension and abdominal pain for one month, and hematochezia for one week.After 10 months, the patient was improved. The hemoglobin level increased to 127 g/L, and β2 microglobulin, urinary kappa chain, and lambda chain returned to normal. Bone marrow biopsy revealed hyperplastic medullary images without neoplastic plasma cells.

5. The authors mentioned patient received one session of inpatient chemotherapy with vindesine， epirubicin and dexamethasone. But what were the specific uses of these important chemotherapy drugs?

Response: Thank you for your question. Vindesine and epirubicin inhibit cell division and prohibit tumor growth. Dexamethasone suppresses autoimmune reactions and has anti-inflammatory effects. This chemotherapy regimen can be used for

amyloidosis.

6. As described in the article, this case had typical gastrointestinal symptoms. Timely diagnoses can help to improve the prognosis of these patients. What are the main differential diagnoses of gastrointestinal diseases?

Response: Thank you for the question. On endoscopy, gastrointestinal amyloidosis can mimic inflammatory bowel disease, ischemic colitis, and gastrointestinal tumors.

7. How to understand “echocardiography revealed myocardial amyloidosis” in follow-up section? Did it mean the progression of the disease? It is a best to give an explanation accordingly.

Response: Thank you for this question. It indicates progression of the disease. This has been clarified in the revised manuscript.

8. Did the patient have any complications during treatment? You would better illustrate whether or not.

Response: Thank you for asking this. Bacterial pneumonia developed during treatment. However, the patient improved after anti-infective therapy.

9. As described in the discussion, the cause of anemia in the present case was gastrointestinal bleeding rather than bone marrow failure due to MM. If so, It could be iron deficiency anemia. Relevant evidence was not mentioned.

Response: Thank you very much for pointing this out. We have addressed this in the revision with the following sentence. The patient had normocytic anemia (HGB 94g/L，MCV 96.40fL，MCH 30.7pg，MCHC 319.0g/L), resulting from acute gastrointestinal bleeding.

10. The diagnostic criteria of SMM are as follows: monoclonal protein level ≥30g/L, 24 hour-urine immunoglobulin light chain ≥ 0.5g, or 10%–60% clonal marrow plasmacytosis with the absence of end-organ damage and biomarkers of malignancy.

It means we cannot diagnose SMM without monoclonal protein level≥30g/L. As described in the laboratory examinations, serum protein electrophoresis and immunofixation were negative. It was inconsistent with the diagnoses.

Response: The sentence has been corrected in the revision. SMM was defined by the presence of either a serum monoclonal protein of ⩾3 g/dL or ⩾500 mg/24 h in urine (or both) and/or ⩾10% bone marrow plasma cells (BMPCs) without evidence of any CRAB symptoms. In our patient，urinary lambda (λ) chain was 1110 mg/L and bone marrow biopsy showed neoplastic plasma cells accounting for 15-20% of the marrow elements, consistent with the diagnosis of SMM.

11. The English writing needs to be substantially improved.

Response: Thank you for your comment. This manuscript has been thoroughly edited by a native English speaker from an editing company again. The certification is uploaded.