

## **Point-by-point responses**

### **Reviewer #1:**

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript aims to describe a case report of gastrointestinal extramedullary plasmacytoma (EMP) of the small intestine with intestinal perforation and abscesses. In the title and the abstract authors claim that they performed a literature review of gastrointestinal EMP, however, in the manuscript, there are no signs of any literature review. The topic is interesting and topical, however, I strongly suggest improvement of the manuscript. Introduction section: I strongly suggest reading the following article »Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations« (Br J Haemato. 2021 Aug;194(3):496-507. doi: 10.1111/bjh.17338) to be more precise with the definition.

**Reply:** Thanks for your suggestion. But after reading this article, I found that this article is about extramedullary(EMD) in multiple myeloma, not extramedullary plasmacytoma(EMP). We have made a more precise definition of EMP according to the similar literature. See"Page 3, paragraph 2, line 3-4"

The authors state « It is a rare type of malignant monoclonal plasma cell lesion, accounting for approximately 3% of all plasmacytomas[1]. It mostly occurs in the upper respiratory tract but is rarely found in the gastrointestinal tract. Gastrointestinal EMP only accounts for approximately 5% of all EMPs[2].« Since the authors claim that they perform the literature review, I would expect that they would be more precise with the data and include the

latest references.

**Reply:** We only did a literature review about Gastrointestinal EMP. Therefore, a more accurate incidence rate of total EMP cannot be summarized. In recent years, many articles have cited these two articles (new [1,2]) as an introduction to EMP incidence, so we have also selected them. See"Page 3, paragraph 2, line 4-8"

The authors state »The small intestine is often the site of gastrointestinal EMP. In addition, the stomach, colon, rectum and appendix may also be affected[3-5].« I strongly suggest reforming the sentence in a way that present the correct situation and the latest knowledge – as far as I know EMP was found in all parts of gastrointestinal tract and based on the data, the small intestine was only one of the sites (see Ann R Coll Surg Engl 2018; 100: 371–376 ).

**Reply:** We have reformed the sentence as your suggestion. See"Page 3, paragraph 2, line 8-9"

I strongly suggest reforming also other sentences in the introduction and discussion section. Namely, many sentences are formed as a final recommendation, which are not. EMP is a rare, thus the authors can state what kind of signs, treatment and outcomes were already reported and for each statement provide the references. In the discussion there are some sentences that do not have any reference and there are sentences that need to have many references and have only one – for instance »Most gastrointestinal EMP is not immediately life-threatening at the time of diagnosis, but it may occasionally progress to plasma cell myeloma, so early diagnosis, treatment and intervention are still needed. Due to the rarity of gastrointestinal EMP, there are no unified treatment guidelines for this disease. At present, complete surgical resection is still the first choice for the treatment of

gastrointestinal EMP. Several studies have reported that patients with gastrointestinal EMP can be completely cured after surgical resection of tumors[19]. Most of the patients underwent routine surgery. However, the EMP patient we reported with perforation of the small intestine required emergency surgery. In recent years, endoscopic treatments such as endoscopic mucosal resection or endoscopic submucosal dissection have become increasingly popular in gastrointestinal EMP surgery and have obtained a good therapeutic effect[20].«

**Reply:** Thanks for your suggestion. We have deleted some sentences that do not have any reference. In addition, we have added more references to the sentences where there was only one reference. See “Page 7, paragraph 2, line 1-4 and line 10-14.”

Figures. please include arrows or circles in the figure to mark the polyp-like protrusion, hyperemia, edema, thickening, and purulent moss. Please also check and correct the second sentence in the legend of figure 2, the third sentence in the legend of fig 1 (C), fig 3 – please provide also a picture of the epithelial part of the small intestine.

**Reply:** We have added arrows in the figure to mark the polyp-like protrusion, hyperemia, edema, thickening, and purulent moss. See “Figure 2”. In addition, we have rewritten the second sentence in the legend of figure 2, the third sentence in the legend of fig 1 (C). See “Page 17, paragraph 1, line 3-5 and paragraph 2, line 2-5.”. We have also added a picture of the epithelial part of the small intestine as your suggestion. See “Figure 3A”

In the title and the abstract, the authors claim that they performed a literature review of gastrointestinal EMP, however, in the manuscript, there are no signs of any literature review. Thus, I strongly suggest performing a review of the reported cases and presenting the results of the literature review in the

table form – showing previously reported cases of gastrointestinal EMP together with all important data (ref, sex, age, location, presentation, treatment, outcome). The manuscript can be significantly improved only if the table of reported cases is a part of the manuscript. Then the authors can refer to case reports and can discuss and make the conclusions.

**Reply:** Thanks for your suggestion. We have added one table which includes the important data (ref, sex, age, location, presentation, treatment, outcome) of reported cases. See “Table 1.”

**Reviewer #2:**

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear Authors' The content from pathology and immunohistochemistry point of view has a few limitations: Microscopic analysis showed that the pathological specimen displayed a large number of neoplastic plasma cells with inflammatory cells infiltration (Figure 3A). These plasma cells were positive for CD38(+), CD138(+), kappa(+), lambda(-), CD3(+), CD68(+), CD79a(+), SDHB(+) and MUM1(+) and negative for CK(-), CD117(-), Dog-1(-), S-100(-), Bcl-2(-), beta-Catenin(-), CD56(-), IgG4(-) and Pax-5(-), with a Ki-67 proliferative index of 10% (Figure 3B-F). Clonality mentioned has both kappa and lambda, which favors a polyclonal proliferation. In addition, the mention of CD3 and CD68 in plasma cells seems inappropriate as CD3 is a T cell marker and CD68 is a histiocytic marker. Hence, the expression profile needs to be reviewed.

**Reply:** Thanks for your suggestion. We have reviewed the the expression profile and corrected some errors and removed some unrelated indicators. See “Page 5, paragraph 2, line 3”

If kappa lambda stands equivocal on IHC, then flow cytometry evaluation remains the gold standard for demonstration of clonality. In addition, the mention of bone marrow being normal is incomplete (especially when the Hb is low) as they have not documented the flow cytometric analysis revealing polyclonal plasma cells. Extramedullary plasmacytomas can have low burden of clonal plasma cells in the bone marrow and such cases may be labelled as MGUS or Smouldering myeloma based on the Serum M protein levels, serum electrophoresis and immunofixation. Lack of lytic lesions must also be furnished to fulfill the criteria of an Extramedullary plasmacytoma.

**Reply:** In addition, we have documented more results of Laboratory and Imaging tests in FINAL DIAGNOSIS section, including "No abnormal monoclonal plasma cells were detected in the flow cytometric analysis. Lytic lesions were not found on X-rays." See "Page 5, paragraph 2, line 8-10."

**Reviewer #3:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: I find the case report interesting and important because EMP perforation is rare and this case adds to our knowledge on outcomes of perforated gastrointestinal EMPs. You state that your case is the first one to describe perforated small intestinal EMP but perforation of the colorectal EMPs has been described. I propose adding it to the discussion in the terms of outcome, more precisely the need for adjuvant therapies.

**Reply:** Thanks for your suggestion. I have added this literature to the discussion. See "Page 7, paragraph 1, line 6-10."

**Re-reviewer 1:**

**Specific comments:** No further suggestions.

**Reply:** Thanks for your comments.

**Re-reviewer 2:**

**Specific comments:** The authors followed suggestions and improved their manuscript significantly. I have only a minor comment. In Table 1 the authors in the outcome column wrote N/A – in the legend please explain what N/A means.

**Reply:** Thanks for your comments. N/A means not applicable.