Peer Review File

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Reviewer A

In my opinion the article is well written, informative and easy to follow. However, I find the title of the article not fully reflecting the presented case. The title indicates a small intestinal MALT lymphoma; yet the discussed clinical case, although showed clear gastrointestinal symptoms, a significant systemic involvement was concomitantly present, and no intestinal involvement was proven by biopsy. As hinted in the discussion, this may be a systemic lymphoma with intestinal involvement rather than the other way around, or paraneoplastic symptoms.
My recommendation would be:

Comment A1: To perform Molecular IGH PCR test on the paraffin embedded sections of both the intestinal and the lymph node sections. Identifying identical B-cell clone in both specimen may support intestinal involvement.

Reply A1: We are grateful to the reviewer for the appreciation of our work and the insightful comments. IgH and IgK PCR (BIOMED2) was performed rather early on, once suspicion for lymphoma became relevant. However, the results of these tests showed a polyclonal pattern. However, in view of the rather low quantity of infiltrating B-cells within the biopsies, a small clonal population may have not been picked up. Therefore, this negative result does not exclude minimal lymphoma infiltration.

Changes in the text: We now mention these PCR results in the text (page 7, lines 145-149): "Indeed, polymerase chain reaction for heavy and light chains (IgH and IgK PCR; BIOMED2) was performed rather early on, once suspicion for lymphoma became relevant. However, the results of these tests showed a polyclonal pattern. In view of the rather low quantity of infiltrating B-cells within the biopsies, however, even a small clonal population may have not been picked up: in this setting, negative results do not exclude minimal lymphoma infiltration" Please see also Reply A2 and related changes in the text.

Comment A2: Modify the title to make it more inclusive for both primary and secondary small intestinal marginal zone lymphoma.

Reply A2: We would like to thank the reviewer for pointing this out. We agree that the small bowel was indeed clinically affected by the lymphoma; however, the origin of the lymphoma remains unclear (no distinction possible between primary intestinal MZL and nodal MZL with secondary spread to the small bowel).

Changes in the text: We changed the title from "Challenges in the diagnosis of small intestinal marginal zone lymphoma: A case report and systematic review of the literature" to "Challenges in the diagnosis of marginal zone lymphoma with symptoms of small intestinal disease: A case report and systematic review of the literature".

Comment A3: Regarding the literature cases- please indicate whether systemic involvement was present or not.

Reply A3: We agree with the reviewer and updated our tables. We considered systemic involvement to be present if stage IV disease was documented. However, in almost half of these cases (47.2%) it was not possible to reliably assess whether systemic involvement was present or not. This was due to either lack of information provided in the case reports or incomplete staging (e.g., CT performed only for the abdomen).

Changes in the text:

- We adapted tables 2 and 3 accordingly, adding information regarding the presence of systemic involvement.
- In the legend for table 2 we added: "Systemic involvement was considered to be present if stage IV disease was documented."
- In the abstract, we added: "In 18.9% of cases systemic involvement was documented." (pages 2 and 3, lines 50-51)
- In the section results we added: "In 18.9% of cases systemic involvement was documented." (page 10, lines 243-244)

Reviewer B

Major comment B1: I think that it would be difficult to diagnose this case as primary small intestinal MALT lymphoma definitely. How did the authors diagnose this case as primary small intestinal MALT lymphoma and exclude the possibility of that small intestine might be an involved site of systemic MZL?

Reply B1: We would like to thank the reviewer for raising this important point. We agree that we cannot distinguish between primary small intestinal marginal zone lymphoma (MZL/ MALT lymphoma) and secondary involvement of the small bowel. Either way is possible.
Also, please compare our reply A2 to reviewer A.

Changes in the text:

- In the section discussion we added: "However, in our case, the distinction between primary small bowel MZL and systemic MZL with secondary involvement of the small bowel is not possible." (page 14, lines 332-333)
- We also changed the title from "Challenges in the diagnosis of small intestinal marginal zone lymphoma: A case report and systematic review of the literature" to "Challenges in the diagnosis of marginal zone lymphoma with symptoms of small intestinal disease: A case report and systematic review of the literature".

Major comment B2: The authors showed that there was no evidence of MALT lymphoma in surgically resected specimen and histological findings of cervical lymph node led to the final diagnosis of MALT lymphoma. Should the surgical resection of small intestine have been performed in this case?

Reply B2: We agree with the reviewer that the best diagnostic approach for MZL has not been clearly defined yet. We believe that our approach was reasonable at that time given that the small

intestinal segment was clearly altered (endoscopic assessment/ visual aspect during laparoscopy). In addition, a sampling error in endoscopic biopsies could be reasonably assumed. However, in retrospect, the resection of a short small bowel segment has indeed been of no clinical benefit as the diagnosis could not be established based on the surgical sample either. This is one of the most important lessons we learned from this case report.
Therefore, the main conclusion we draw from this case is that an early PET/CT scan might serve as a valuable diagnostic tool when MZL is suspected. In our case, it might have spared the patient the surgical intervention.

Changes in the text:

- In the section conclusion: "In particular, a 2-[^{18}F]FDG-PET/CT might help to establish the diagnosis if repeated endoscopic sampling remains unsuccessful and has the potential to spare the patient more extensive interventions including intestinal surgery." (page 17, lines 425-427).

Major comment B3: Ileum end have been reported to be common site of primary gastrointestinal lymphomas. Although the authors showed that the ileum was the most common site in their systematic review, how was the frequency of involvement of ileum end?

Reply B3: We feel this is an important suggestion: involvement of the terminal ileum, a part of the intestine in the reach of ileocolonoscopy, is important since routine endoscopy can establish the diagnosis.

Changes in the text: We have incorporated this suggestion in table 3, as well as in the text: "The terminal ileum was involved in 15.7% of cases". (page 10, lines 236-237)

Minor comment B1: Lugano stage should be added, if the authors diagnosed this case as primary small intestinal MALT lymphoma.

Reply B1: Assuming that the small bowel was indeed affected by the lymphoma, its origin still remains unclear (no distinction is possible between primary intestinal MZL and nodal MZL with secondary spread to the small bowel). In either case, there would be stage IV disease according to the Lugano classification.

Changes in the text:

- In the section case presentation we added "We could not formally distinguish between primary intestinal MZL and nodal MZL with secondary spread to the small bowel. Assuming that the small bowel was indeed affected by the lymphoma, there would be stage IV disease according to the Lugano classification." (page 8, lines 173-175)
- We changed table 2 indicating that in our case (the last line in the table) systemic involvement was present.

Minor comment B2: The authors should write "small intestinal MALT lymphoma", not "small intestinal MZL".

Reply B2: Throughout the literature "intestinal MZL" and "intestinal MALT lymphoma" are widely used to describe the same entity. For our understanding "small intestinal MALT lymphoma" and "small intestinal MZL" are synonyms and we did not change the wording.

Changes in the text: In the introduction, we clarified the wording and added the following sentence: “In the literature, the term “intestinal MALT-lymphoma” is often used synonymously for “intestinal MZL”. In this article we use the term “small intestinal MZL” to describe MALT-lymphoma/ MZL of the small bowel.” (page 4, lines 68-71).

Minor comment B3: Rituximab-containing chemotherapy should be noted as "immunochemotherapy".

Reply B3 and changes in the text: Thank you for your suggestion. We implemented the proposed changes throughout the text and in table 2.

Minor comment B4: Table 2 seems to be too complicated. The authors should change Table 2 to make it more simply and understandable.

Reply B4 and changes in the text: We agree with the reviewer, table 2 seems overly complicated. We have therefore reworked and simplified table 2. We hope these revisions improve the clarity of our data presentation.

Minor comment B5: The authors need to add immunohistological findings of CD5, CD10, and cyclin D1 in Figure 4.

Reply B5: We agree with the reviewer. Resection of a metabolically active cervical lymph node confirmed partial involvement by a marginal zone lymphoma. The histological examination revealed a focal marginal zone-like growth pattern of clonal B-lymphocytes (as detected by clonal immunoglobulin heavy chain/IgH rearrangement) with a so-called “null phenotype” (no expression of CD5, Cyclin D1, CD23, bcl-6 and CD10).

Changes in the text:

- In the section case presentation we added: “no expression of CD5, Cyclin D1, CD23, bcl-6 and CD10)” (page 8, lines 170-171)

Minor comment B6: The authors should explain what the vertical and horizonal axis indicates in detail in Figure 5.

Reply B6 and changes in the text: We agree with the reviewer that the axis labels need clarification. We now clarify in detail in the legend to figure 5 (page 32, lines 783-784) the significance of each axis. We hope that these changes will facilitate the readability of this figure.

Reviewer C

The authors present a well written manuscript on the rare and oncologically interesting entity of marginal zone lymphoma in the small bowel. It is an extensive overview on individual cases and challenges in diagnostic workup in small intestinal marginal zone lymphoma.

Resubmission after minor revision is recommended.

Comment C1: Radiation as a treatment option is mentioned in the abstract under results, but also should be described within the text. The largest cohort published with regard to radiotherapy in intestinal lymphoma should be cited (Reinartz G, Molavi Tabrizi C, Liersch R, et al. Renaissance of Radiotherapy in Intestinal Lymphoma? 10-Year Efficacy and Tolerance in Multimodal Treatment of 134 Patients: Follow-up of Two German Multicenter Consecutive Prospective Phase II Trials. Oncologist.2020;25(5):e816-e832. doi:10.1634/theoncologist.2019-0783).

Reply C1 and changes in the text: We are grateful to the reviewer for the appreciation of our work and for providing these insights. We agree, that this aspect should be added to the text (discussion).
We have added a new paragraph (pages 16 and 17, lines 398-413) mentioning the role of radiation therapy in intestinal lymphoma treatment and the results of our review in this regard. The references have been updated accordingly (page 30, lines 729-732).

Reviewer D

Comment D1: Please specify the type of this article: review or case reports. The format of this manuscript does not fit the general style of review articles or case reports.
1-1. If the authors intend to write a narrative or systematic review article, they should remove the case presentation section and rewrite the manuscript.
1-2-1. If the authors intend to write a case report, the authors should describe the uniqueness of the case and how the case contributes to the existing literature. Particularly, in the Abstract, the authors should focus on the similarities and differences between the present case and the previously reported cases. In addition, the conclusion section should be brief and provide a conclusion with recommendations and applicability to practice that the authors learned from the presented patient.
1-2-2. It is recommended that case reports be submitted to journals dedicated purely to case reports, since case reports do not include controls, have limited sample size (one to a few individuals), and are unblinded, limitations that require a cautious approach to interpretation of findings.

Reply D1:
The reviewer raised an important point, which applies to the study of all rare diseases. On the one hand, small bowel MZL is a rare clinical entity. Our case illustrates the difficulties and pitfalls in the diagnostic management of small bowel MZL. Moreover, the case highlights the importance of a multidisciplinary approach and provides a potential solution if endoscopy does not allow a final diagnosis. We are therefore convinced that our case is worth publishing and should not be removed from our manuscript.
On the other hand, the review provides a comprehensive overview on the variable clinical presentation and management of this rare entity. The 52 cases from the literature provide an equivalent of a well-characterized patient cohort which will clearly be of interest to the field.

We therefore believe that the case report and the review should not be separated as they go hand in hand and complement each other. Having the review data together with our illustrative case report is, in our view, of great benefit to the reader. In our opinion, this is the only way to successfully study rare diseases, such as MZL with small bowel manifestations.

However, we agree with the reviewer that the manuscript should be modified: the uniqueness of the case and how the case contributes to the existing literature should be better described. We also added conclusions and lessons learned from the case to the abstract and to the conclusions. We also agree that the conclusions should be brief and we therefore shortened the wording.

Changes in the text:

- In the abstract we added: "Remarkable in this case was the long diagnostic delay. Small bowel histology was negative despite repetitive endoscopic sampling and even surgical resection of macroscopically affected tissue. However, after diagnosis the response to systemic treatment was excellent". (page 2, lines 40-43)
- In the conclusion we added: "In particular, a 2-[18F]FDG-PET/CT might help to establish the diagnosis if repeated endoscopic sampling remains unsuccessful and has the potential to spare the patient more extensive interventions including intestinal surgery." (page 17, lines 425-427)
- In the conclusion we deleted the following: "Multiple rounds of endoscopies and/or intestinal surgery with sampling are often necessary." (page 17, line 422)

Comment D2: Lactate dehydrogenase level should be mentioned, since it is included in the MALT-lymphoma International Prognostic Index.

Reply D2 and changes in the text: We agree with the reviewer, LDH is indeed an important prognostic factor. The LDH level is now mentioned in the case presentation (page 6, line 118)

Comment D3: It is recommended that H. pylori infection status be described.

Reply D3 and changes in the text: The H. pylori status is now mentioned in the case presentation (page 6, line 125)