Responses to reviewers

Dear reviewers,

Thank you for the comments concerning our manuscript (NO: 76161).The title is “A rare primary rectal MALT lymphoma with curative resection by endoscopic submucosal dissection: a case report and minireview”. We appreciate to you for suggesting how to improve our paper. We have read your comments carefully and made correction. We hope this revision meets with your approval.

Reviewer #1:

The authors presented a rare case of rectal MALT lymphoma that underwent ESD as a sole treatment. This case report is very interesting; however, some detail in the manuscript should be clarified. -The conclusion in the abstract should be revised. The sentence “This case provides a reference for the diagnosis and treatment of mucosa-associated lymphoid tissue lymphoma originating in the digestive tract.” might be overstated. From my point of view, the authors might conclude that ESD is safe and effective for rectal MALT lymphoma.

Response: Thanks for the reviewer’s suggestion. We have modified these sections as reviewer suggested in the revised manuscript.

The conclusion in the abstract had been modified as reviewer suggested in the revised manuscript. ESD is a safe and effective therapeutic option for rectal mucosa-associated lymphoid tissue lymphoma.

-The authors used NBI and chromoendoscopy to diagnose this lesion, so they should state the NICE, JNET, and Kudo's classification. What was the endoscopic diagnosis at that time?

Response: Thanks for the reviewer's suggestion. We have increased these sections as reviewer suggested in the revised manuscript.

In our case, the lesion was classified as NBI international colorectal endoscopic (NICE) type 3, Japanese NBI expert team (JNET) type 3, and Kudo Pit Patterns type V_N. On the basis of dendritic and grid-like irregular microvessels and pit pattern structure disappeared on the surface of the lesion in magnifying endoscopy, the rectal lesion was diagnosised as lymphoma. At the same time, biopsy specimen had been taken to pathological examination.

-The EUS image should be enlarged and clearer. It is crucial for treatment consideration (Endoscopic resection vs Surgery). From this EUS image, it was very difficult to determine what colonic layer that tumor invaded through.

Response: Thanks for the reviewer's suggestion.

Hypoechoic thickening of the mucosal layer was detected by endoscopic ultrasound. The lymphoma invades the mucosal layer inside that has been

confirmed by pathological examination of ESD specimen. Unfortunately, the magnified EUS images could not be recorded because of limitations of outdated endoscopy equipment.

-The authors should clarify the endoscopic diagnosis. Did the authors diagnose this lesion as rectal lymphoma from colonoscopic findings and perform the ESD?

Response: Thanks for the reviewer's suggestion. We have modified these sections as reviewer suggested in the revised manuscript.

In our case, on the basis of dendritic and grid-like irregular microvessels and pit pattern structure disappeared on the surface of the lesion in magnifying endoscopy, the rectal lesion was diagnosised as lymphoma. At the same time, a biopsy specimen was taken from the lesion and confirmed histologically as mucosa-associated lymphoid tissue lymphoma. Later, the patient underwent curative ESD to treat the lesion.

-Was there any difficulty during ESD for rectal MALT lymphoma (ex. adhesion)? Any tips for resecting this kind of lesion?

Response: Thanks for the reviewer's suggestion. We have added these sections as reviewer suggested in the revised manuscript.

In our case, no obvious adhesions were found during ESD procedure. Before resection, the characterize of lesions and their architecture should be fully

evaluated with the help of abdominal CT, NBI, EUS and other techniques. EUS and submucosal injection of normal saline may be helpful to evaluate the infiltration depth of the lesion. The tumor lesion above muscularis propria should be completely resected during ESD.

-What is the surveillance protocol for PET-CT, EUS, and colonoscopy? Please explain.

Response: Thanks for the reviewer's suggestion. We have added these sections as reviewer suggested in the revised manuscript.

Considering this MALT lymphoma case is a low-grade malignant tumor and has been completely resected, a reasonable follow-up strategy was made after discussion with hematologists , pathologists and patient. The endoscopy and lymph node ultrasound review at 6 and 12 months and PET-CT at 12months after ESD were carried out. When no suspicious lymphoma lesions were found, we decided to review colonoscopy, EUS, and lymph node ultrasound annually.

Reviewer #2:

Specific Comments to Authors: This manuscript is a case report of a patient with rectal MALT lymphoma which was treated by endoscopic submucosal dissection. Endoscopic findings and treatment strategy has not fully discussed yet as colorectal lymphoma is a rare condition. This topic will likely be of

interest to clinicians in the field. However, I have serious concerns with this manuscript as described below.

Major 1. I think this case of MALToma is rare in terms of rectal origin and endoscopic resection. The authors should emphatically discuss those points including data quoted from related literatures.

Response: Thanks for the reviewer's suggestion. We have modified these sections as reviewer suggested in the revised manuscript.

We've added to the discussion about MALT lymphoma is rare in terms of rectal origin and endoscopic resection.In a review of literature, Dionigi et al found primary colorectal lymphoma to account for only 0.2 % of all malignant tumors of the colorectum. The colon and rectum are the least common gastrointestinal locations for primary lymphoma, accounting for <10% of gastrointestinal lymphomas. Colorectal MALT lymphoma is an even rarer disease. Colorectal MALT lymphoma comprises only 2.5% of MALT lymphomas. This is especially true in this case, as laterally spreading tumour-like elevated lesions are even rarer.

Approximately 33% of patients with colorectal MALT lymphoma receive endoscopic mucosal resection. There are few reports about ESD in the treatment of colorectal MALT lymphoma. Ahlawat S et al. reported 30 patients with rectal MALT lymphomas, including 5 patients managed solely with EMR. Deeper lesions have usually been treated surgically

2. The readers should be interested in the treatment strategy for colorectal MALT lymphoma. The authors should expand discussion regarding the treatment strategy.

Response: Thanks for the reviewer's suggestion. We have modified these sections as reviewer suggested in the revised manuscript.

We've added to the discussion discussion regarding the treatment strategy.The treatment modalities include surgical resection, etiopathogenetic therapies, chemotherapy, chemoimmunotherapies, radiation, and endoscopic resection, while most cases use surgery or chemotherapy as the first-line treatment. A review of 51 cases of the MALT variant of primary rectal lymphoma revealed significant differences in treatment modalities. A complete response was achieved in 12 of 19 cases treated with *Helicobacter pylori* eradication therapy, 5 of 6 with radiation, 2 of 4 cases with chemotherapy, 2 of 4 with endoscopic resection, 6 of 8 cases with surgical resection, and all 8 with combination therapies. In most cases, tumor resection or chemotherapy is used as the primary treatment. Remission rates of resection and chemotherapy were higher than 90%. Radical surgery or local excision showed 5.3% treatment failure at first-line treatment.

Minor 1. (P2L11) "HE" should be replaced "hematoxylin and eosin".

Response: Thanks for the reviewer's suggestion

Please forgive our mistake. We have modified this section. “HE” has be replaced “hematoxylin and eosin(HE)”.

2. (P2L15) Please delete “In conclusion”.

Response: Thanks for the reviewer’s suggestion

Please forgive our mistake.We have deleted “In conclusion” in the revised manuscript.

3. (P3) Chief complaints is too long. I think “asymptomatic” or “for further examination and treatment” are suitable.

Response: Thanks for the reviewer’s suggestion

Please forgive our mistake. We have shortened chief complaints in the revised manuscript.

4. Please describe how *H. pylori* infection was denied.

Response: Thanks for the reviewer’s suggestion

Please forgive our mistake. We have described that the 13C-urea breath test tested negative for *H. pylori* in the revised manuscript.

5. The authors should describe laboratory results in detail including LDH and sIL-2R.

Response: Thanks for the reviewer’s suggestion.

Please forgive our mistake. We have described that laboratory results of lactate dehydrogenase, hemoglobin, plasmacytic differentiation and soluble interleukin-2 receptor showed no obvious abnormalities in the revised manuscript.

6. (P5L12) Please replace “mucous” with “mucosal”.

Response: Thanks for the reviewer’s suggestion.

Please forgive our mistake. We have replaced “mucous” with “mucosal in the revised manuscript.

7. (P5L12) Please explain the EUS finding of submucosal invasion.

Response: Thanks for the reviewer’s suggestion.

In our case, hypoechoic thickening of the mucosal layer was detected by EUS, and no submucosal invasion. The histopathological findings of the ESD specimen showed the lymphoma invades the mucosal layer inside.

8. The authors should describe the depth of tumor in histopathological examinations.

Response: Thanks for the reviewer’s suggestion.

We have described the lymphoma invades the mucosal layer inside in histopathological examinations in the revised manuscript.

9. I recommend that the final diagnosis should be placed after the treatment section.

Response: Thanks for the reviewer's suggestion.

We have placed the final diagnosis after the treatment section in the revised manuscript.

10. There are too many images. Please delete unnecessary ones.

Response: Thanks for the reviewer's suggestion.

In some way, we consider that these images are very important for the diagnosis and differential diagnosis of rectal MALT lymphoma. These detailed images may be used as a reference for other clinicians.

11. (P10L16-17) It's difficult to understand the sentence, "The lesion also is….".

Response: Thanks for the reviewer's suggestion.

Please forgive our mistake. We have modified this section. "The lesion also is…." is deleted in the revised manuscript.

Reviewer #3:

Specific Comments to Authors: Manuscript NO: 76161 Title: A rare primary rectal MALT lymphoma with curative resection by endoscopic submucosal dissection: a case report and minireview The authors reported a case of a

patient with rectal MALT lymphoma with curative resection by endoscopic submucosal dissection. A report of patients with primary rectal MALT lymphoma is a welcome addition, as this is an infrequent disease. I think however that there are a few improvements that should be made before publication. 1. The first time the authors use an abbreviation in the text, present both the spelled-out version and the short form. For example, "HE", "PET-CT", "MRI" are not defined.

Response: Thanks for the reviewer's suggestion.

Please forgive our mistake. We have modified this section. We have defined them when "HE", "PET-CT", "MRI" were first used in the revised manuscript.

2. "Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue" is the proper name of MALT lymphoma.

Response: Thanks for the reviewer's suggestion.

Please forgive our mistake. We have modified this section. We have defined MALT lymphoma as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the revised manuscript.

3. "Helicobacter pylori" should be italicized.

Response: Thanks for the reviewer's suggestion.

Please forgive our mistake. We have modified this section. We have modified "Helicobacter pylori" to italics (*Helicobacter pylori*) in the revised manuscript.

4. Involvement of other organs should be exluded before the diagnosis of MALT lymphoma localized to the rectum. For example, CT (or PET-CT), esophagogastroduodenoscopy, bone marrow examinations seemed to be requred in the present case. It is recommended that the results of these examinations be described prior to the "FINAL DIAGNOSIS" in the manuscript.

Response: Thanks for the reviewer's suggestion. We have modified this section. in the revised manuscript.

Other examinations of the patient including enhanced computed tomography, positron emission tomography-computed tomography (PET/CT), bone marrow biopsy and gastroscopy showed no obvious abnormalities.

Re-reviewer' comment:

The revised manuscript is improved. However, several concerns remain unresolved. 1. The authors should describe your opinion in treatment strategy for rectal MALT lymphoma based on the results of the presented data and guidelines of MALT lymphoma in other organs. For example, firstly, H. pylori eradication can be attempted; secondly, ESD should be attempted in case of localized, mucosal lesion; other localized lesions should be treated by surgical resection or radiotherapy and/or chemotherapy, and so on. A flowchart can help readers understanding. 2. "Lymphoma" should be inserted after "(MALT)" in sentences in Abstract, Core Tip and Introduction. 3. The content of chief complaints and history of present illness is overlapped. It should be modified. 4. The first three sentences in Discussion section should be described in Introduction section. 5. There are too many images. Please delete unnecessary ones. I think that at least Figure 2A-C and Figure 5 can be deleted as they have little information.

Dear Editors, We have revised our manuscript (76161_Auto_Edited) again according to the 76161_Revision Review Report. First, thanks for the reviewer's suggestion. We have inserted "Lymphoma" after "(MALT)" in sentences in Abstract, Core Tip and Introduction, and have put the first three sentences of Discussion section in Introduction section. Second, chief complaints and history of present illness have been modified. Third, we have describe our opinion in treatment strategy for rectal MALT lymphoma based on the results of the presented data and guidelines of MALT lymphoma in Discussion section. Finally,we have deleted the original figure 2C. The original figure 2A, B,D show that the mucosal layer clingingto the muscularis propria were completely resected and no obvious adhesions were found during the ESD procedure. It also reminds clinicians that the tumour lesion above the muscularis propria should be completely resected during ESD. Figure 5 shows the patient no recurrence without any additional treatment for 2 years after the endoscopic procedure.The modified 76161-Figures.pptx has been re-uploaded along with the revised manuscript.

Thank you and best regards.

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