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ANSWERING REVIEWERS

Name of journal: World Journal of Gastroenterology

Manuscript NO: 58225

Title: Case report: Multiple cerebral lesions in a patient with refractory celiac disease

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Reviewer's code: 03815241
Position: Peer Reviewer

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Enteropathy-associated T cell lymphoma (EATL) is a rare condition associated sometimes with refractory celiac disease The involevement of the brain is even more rare. Your manuscript is well written with no plagiarism. It could be published as a rare condition

ANSWER:

Thank you! We appreciate the positive feedback.

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Reviewer's code: 03505676
Position: Editorial Board
Academic degree: MD, PhD

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Refractory celiac disease (RCD) has been subdivided into 2 subgroups (RCDI and RCDII) according to the normal or abnormal phenotype of intraepithelial lymphocytes (IELs), of which RCDII is considered as a low-grade intraepithelial lymphoma and has a poor prognosis due to gastrointestinal and extraintestinal dissemination of the abnormal IELs, and high risk of overt lymphoma. Enteropathy-associated T cell lymphoma (EATL) frequently evolves from RCD II. In the study, the authors reported an extraordinary case of EATL with multiple cerebral lesions in a patient with RCD and suggested a diagnostic possibility when a patient with known RCD presents with neurological deterioration. This report presented a clinical value for the management of RCD. If possible, after gaining an ethical Consent, the researcher could perform a genomic analysis or immunological markers including IL-15 and feature a unique profile of such patient population. Moreover, some potential novel treatment strategies for a better prognosis of this lethal

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complication of coeliac disease should be supplemented in the discussion section.

ANSWER:

We thank the reviewer for his/her positive feedback and the constructive remarks. As the patient had deceased at the time point of writing this case report, additional post-hoc genetic/immunologic analysis were unfortunately not feasible.

In response to your comment and those from other reviewers we now added information on novel treatment strategies for EATL in the discussion section; line 200-207.

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Reviewer's code: 03656577
Position: Peer Reviewer

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Cerebral involvement in EATL is extremely rare in clinics. In this manuscript, the authors describe such a kind of disease in patients with RCD. It is a good written report, which included various details of the cases, so it will provide an extraordinary value for others to learn from it. However, in the discussion part, some novel strategies (e.g. clinical trials?) for CD or RCD could be discussed.

ANSWER:

Thank you for the positive feedback and your suggestion.

In this case report we set the focus on EATL and particularly the complication of cerebral metastasis. In our point of view, to further outline therapeutic options of CD and RCD would go beyond the scope of this case report. However, also in response to comments from other reviewers, we expanded the section on novel therapeutic attempts for PTCL including EATL, line 200-207.

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Reviewer's code: 03664074
Position: Peer Reviewer

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript has reported a case about a died patient with neurological symptoms induced by enteropathy-associated T cell lymphoma (EATL). It is rare and clinical point, so this experience should be introduced to related people. But there are some problems existing in the manuscript. 1) As the author mentioned in the case presentation and discussion, where are the figure 5 and 6 displayed? 2) All figures' magnification or diameter was not demonstrated. 3) In the Figure 2 C and D, negative/positive standard both of TIA-1 and CD8 on Intraepithelial lymphocytes is not unified. 4) In the Figure 4 C and D, the bar should be used to identify the CD3 positive lymphoma cells and non-malignant T lymphocytes.

ANSWER:

Thank you for these important remarks and your generally positive feedback.

Point 1: We corrected the mistake and changed "Figure 5" to "Figure 4B" and changed "Figure 6" to "Figure 4 C/D".

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Point 2: We now added the diameter in the histological figures.

Point 3: We now added the respective arrows.

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Reviewer's code: 02439215
Position: Peer Reviewer

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1.The extension and thinking of cases are not enough. Although a new case of EATL characterized by cerebellar and brainstem involvement is proposed in this paper, which provides ideas for the clinical differentiation and diagnosis of EATL, the clinical connection, pathogenesis and therapeutic effect of EATL are not deep enough. The possible mechanism of EATL involving CNS, the possible early diagnostic indicators, the treatment of EATL with CNS, and the method to solve poor clinical prognosis of this disease should be further considered and explored in order to enlarge the clinical value of the article as much as possible. 2.There are some problems in the use of words and sentences. A large number of long sentences are used in this paper, but there are some deficiencies in the use of some long sentences. For example, the second sentence of "Core tip" may not be properly expressed in English; if "and" in the last clause of "Case summary" is replaced with "but", it may be more logical. There are many inappropriate words and sentences in the article. Therefore, the writing and the use of words and sentences need to be further modified

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to strengthen the coherence and logic of the article. 3.The description of the case in the "Case introduction" in the article may need to be more detailed, including medical history, clinical examination, etc. The article may simply outline the case through some positive symptoms. If the content can be more enriched, it would be good. 4.In the case introduction, there is a serial number error, and there is a lack of 3 between (2-4). 5.The author only describes the patient's psychiatric symptoms without describing the relevant signs. 6.For important laboratory results, there is no detailed description of specific values. 7.The description of the treatment drug does not have a specific dosage and duration of use. 8.The time sequence in the case summary is chaotic, and the brain biopsy results should be described after the death of the patient. 9. No corresponding new treatment methods have been proposed: such as monoclonal antibodies, the possibility of interferon therapy. 10.The research background of EATL has not been introduced in detail, such as the incidence rate, which organs are easily invaded outside the intestine, etc. 11.There are doubts about the diagnosis of type II RCD in patients. Stomach pain, weight loss, and postprandial abdominal distension should be considered as EATL before 6 months.

Answer:

We thank the reviewer for the positive feedback and his/her constructive remarks.

Point 1: We now added a possible mechanism of EATL involving CNS; line 164. Possible early diagnostic indicators such as FDG-PET/CT scan, repeated cerebral MRI, CSF analysis - as mentioned in section 6) - with simultaneous consideration of the histologically confirmed EATL from intestinal resection specimen lead to a high clinical suspicion of malignant CNS involvement. Possible treatment options of EATL with CNS involvement are already mentioned in the treatment section; line 208-211. We adapted the conclusion part and mentioned a possibility to improve the clinical prognosis; line 228-229

Point 2.: We changed the sentence in "core tip" and adapted the last sentence in "case summary". We applied some minor changes in wording throughout the manuscript, all of which are marked in red.

Point 3: We now added that there were no relevant past illnesses. Concerning medical examination, we now

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added that besides a tender abdomen, there were no abnormalities.

Point 4: We now corrected the error mistake.

Point 5: The neurological signs and symptoms such as gait ataxia, undirected dizziness, double vision and cognitive impairment as an expression of supra- and infratentorial involvement are highlighted in line 114 and 115.

Point 6: We now added information on general laboratory results. However, we do not go into detail about certain laboratory values as all of them were within the normal range and without especial informative value for the clinical course of the patient.

Point 7: We now added the total dosage of methotrexate and that it was administered as single dose.

Point 8: The brain biopsy was performed before the patient's death; therefore we would prefer to keep the actual sequence.

Point 9: In response to your comment as well as recommendations of other reviewers, we now added information on targeted therapy approaches in PTCL including EATL; line 200-207.

Point 10: We now added the incidence rate. Concerning the forms of clinical manifestation, e.g. extraintestinal organ involvement, we would like to refer to line 157-162.

Point 11: Thank you for this remark. The symptom triad (weight loss, postprandial bloating, abdominal pain) was compatible with either diagnosis of RCD or malignancy. However, histological examination of the macroscopically ulcerative jejunitis pointed out the diagnosis of RCD II and therefore the patients was treated concerningly.

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The current manuscript reported a case rarely reported previously discribed as EATL with cerebral involvment in a RCD patient. The topic is interesting, and the clinical proof is abundant. I have some concerns to improve this manuscript: 1. in Line 63-64, the authors referred the gamma delta T lymphocte immunophenotyp, but I did not find any pathological data to support that phenotype through the manuscript. 2. in Line 100, as to the jejunal biopsies, why did not operate this biopsy soon after the capsule endoscopy examination, for example, by intestinal endoscopy?

ANSWER:

Thank you for the positive feedback and remarks.

Point 1: We addressed this finding in the "morphology" section in the discussion.

Point 2: After detection of the ulcerative jejunal lesions in capsule endoscopy, push-endoscopy including biopsies was performed. To clarify this procedure for the reader, we changed the wording in line 100-102.

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Science editor:

SUPPLEMENTARY COMMENTS

This is an unsolicited manuscript. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. 5 Issues raised:

(1) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

(2) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

(3) Please add "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" section to the main text, according to the Guidelines and Requirements for Manuscript Revision; and

(4) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

ANSWER:

Thank you for the positive feedback!

Point 1. We now provide the original figures in a power point file.

Point 2. We now changed the citation style analog WJG style, including DOI and PMID.

Point 3. We now added these chapters.

Point 4. We refer to answer 2.