Author’s response to reviews

Title: Methotrexate-associated lymphoproliferative disorder in the stomach and duodenum: A case report

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Cecilia Devoto, BSc, MSc, PhD
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Dear Dr. Cecilia Devoto:

Re: Manuscript reference No. BMGE-D-18-00392

We are grateful for the opportunity to revise our manuscript titled “Methotrexate-associated lymphoproliferative disorder in the stomach and duodenum: A case report” and for the helpful comments provided by the reviewers.
We have attached a version of our manuscript with revisions shown using tracked changes as well as point-by-point responses to the reviewers. We believe that the comments have allowed us to improve our manuscript, and we are grateful to the reviewers. Revisions in the text are shown using yellow highlight for additions and strikethrough font for deletions.

We hope that the revisions in our manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Gastroenterology.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

1. Line 41, page 1: I am not sure I understand what authors mean when they say: "but chemotherapy based on tissue type is required in intractable or recurrent cases". It may be more appropriate to say "chemotherapy may be needed to treat lymphoma recurring or persisting after stopping MTX treatment".

2. Line 41: Lymphoma treatment does not depend on tissue type.

Response: Thank you for pointing this out. We have changed the sentence in line 9 of the Background.
3. Line 54; Discussion page 1: Withdrawal of MTX results in spontaneous remission of LPD in 25-60% of cases. Please comment how long does the remission last and how many require further treatment with chemotherapy like your patient.

Response: Certainly, we have added information about the remission duration and the rate of necessity of further treatment in the Discussion and conclusions.

4. Line 22; Discussion page 2: Please add data if available about the incidence of lymphoma in RA patients following use of other agents in RA: Cyclosporine, Biologicals etc. Is it higher than baseline lymphoma rate in general population as well as RA patients not on these drugs?

Response: We will add the data about cyclosporine. Since there are only case series about biologicals, we do not have any accurate data. Nonetheless, we will add the information about the case series of biologicals.

5. Figure 3: Add SUV values for the serial PET scans, if available.

Response: Certainly, we will add SUV values.

6. Table 1: Remove this table as it does not add much value since most values are normal except sIL2R(already nicely graphed in figure 3) and LDH.

Response: We have deleted the table.

Responses to the comments of Reviewer #2

1. The keywords include Epstein-Barr virus. It would be better to remove Epstein-Barr virus (EBV) to stress that the reported case is instead classified as a MTX-LPD. Nevertheless the reported patients tested negative for EBV (i.e., ISH negative).

Response: We have deleted the key word.

2. Since this report describes a single case, the therapeutic effect of the chemo-immunotherapy (i.e., R-CHOP) on LPD as well as RA could be considered
Response: In our case, remission could not be maintained by withdrawal of MTX. We thought that complete remission could be achieved by chemotherapy.

3. Of note, it could be useful to describe the differentiated WBC count with particular regard to lymphocyte count.

Response:

Recent studies have suggested that the early recovery of the absolute lymphocyte count after withdrawal of MTX is associated with the spontaneous regression of MTX-LPD.

We have added the data about the transition of the lymphocyte count.

4. Consistent with point 1, the discussion on EBV-LPD could be shortened.

Response: We have shortened the discussion about the relationship between EBV and LPD.

5. With regard to ISH studies, it could be better to report the % of positivity.

Response: We are not sure we understand whether "the % of positivity" means "in the previous study, the positive rate of EBV in MTX-LPD patients" or "the expression rate of EBV-ISH in our case". Regarding the former, we added the statement “the prevalence of EBV in RA patients with LPD was significantly higher than that in sporadic LPD (27.6% vs. 9.9%).” at line 33 of the Discussion and conclusion. Regarding the latter, EBV-ISH was negative in our case. If you mean the latter, we will add “0%” after “Epstein–Barr virus (EBV)-encoded small RNA in situ hybridization (ISH) demonstrated that the EBV was absent” at line 21 of the Case presentation.

6. It could be discussed that CD5+DLBCL is associated with a more aggressive outcome with respect to CD5-DLBCL

Response: We have added the information about the aggressive outcome of CD5-positive DCLBCL.