Author’s response to reviews

Title: Successful treatment of primary bone marrow Hodgkin lymphoma with brentuximab vedotin: a case report and review of published reports

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Manuscript title: "Successful treatment of primary bone marrow Hodgkin lymphoma with brentuximab vedotin: a case report and review of published reports"

Dear Dr. Eşkazan,

Thank you for your review dated 12 March 2018. We appreciate the careful review and constructive suggestions. Based on the instructions provided in your suggestions, we would like to resubmit a revised copy of our manuscript.
Please find below our point-by-point responses to the comments raised by each reviewer. We agree with all of the comments raised by the reviewers. We would like to take this opportunity to thank the reviewers for their constructive and useful remarks. Their comments allowed us to identify areas in our manuscript that needed modification and clarification.

We hope that the revised manuscript is accepted for publication in the Journal of Medical Case Reports.

Yours sincerely,

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Reviewer #1

This is a nicely written case report than can add a therapeutic option for patients with primary bone marrow Hodgkin lymphoma. However, histopathological figures are drawn with very poor quality and cannot be reviewed. Please add them as a TIFF image.

The reviewer pointed out low resolution of histopathological figures.

We have changed the figures from JPEG to TIFF images and we attached high resolution TIFF image (dpi 600).

Reviewer #2

DISCUSSION:

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:
   - De-identified demographic information (age, gender, ethnicity)
   - Main symptoms of the patient
Medical, family and psychosocial history --> Medical and social history is limited and can be improved. No family history is included.

Relevant past interventions and their outcomes --> Please see comments to authors

We have added the patient’s family history.

Kindly address the comments below:

1. Background section, Line 3 - Consider Rephrasing - e.g., Shah et al reported a case of HIV associated PBMHL. Since it is an case report and ideal to avoid strong comments based on such irrespective of that authors verbiage

We have modified the text as follows:

“However, Shah et al. (3) reported a rare case involving a patient with “primary bone marrow” Hodgkin lymphoma (PBMHL) with human immunodeficiency virus (HIV).”

2. Case presentation, Line 32 - briefly mention prior therapy for Burkitt lymphoma as it is always relevant

We have briefly mentioned prior therapy for Burkitt lymphoma.

3. Line 33 - smoking history should be given in pack years

We have changed “20 cigarettes per day” to “18 pack-years.”

4. Line 36-39 - Not necessary as it does not add any value

We have removed these sentences.

5. Line 41 - Consider Rephrasing - e.g., "Physical exam was normal except for…”

We have revised the text as follows:

“Physical examination findings were normal except for small papules on his upper back.”

6. Line 43-44. HIV Status should be reported in this context in the wording as well.
We have added the HIV status.

7. Line 49 - "and he was FOUND to be EBV-Positive"

We have revised the text as follows:

“he was found to be EBV-DNA-positive”

8. Line 56 - "However, EBV-DNA TURNED positive"

We have revised the text in accordance to your instruction.

9. Was a PET/Scan done at any point, as it is an important tool particularly in Hodgkin lymphoma

We have added the following sentence:

“Positron emission tomography/CT was unavailable for financial reasons.”

10. Important therapy-related questions:

a. Is there evidence for the use of DeVIC chemotherapy in such setting? If so, kindly provide reference with brief discussion.

b. Outcomes with AVD/CHOP-like regimens may have had inferior outcomes in this setting due to nature of the disease. Particularly, ABVD is the best available treatment regimen for HL in general and may not be easily replaced as first line choice by DeVIC. This has to be discussed in more depth why it was chosen.

Mainly because of the rarity of this disease, there is no established evidence for the efficacy of DeVIC. However, previous reports have shown the ineffectiveness of ABVD in our settings. We considered that this ineffectiveness might be caused by the multi-drug resistance-1 gene.

We have revised the text as follows:

“Because some patients with EBV-associated lymphoproliferative disease express P-glycoprotein, which is a multi-drug resistance-1 (MDR1) gene product (12), the poor prognosis of PBMHL may be related to the presence of the MDR1 gene. DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) includes ifosfamide and carboplatin, which are MDR-unrelated anticancer agents. In addition, because of coexisting pulmonary emphysema, DeVIC therapy was initiated at 12 weeks from onset.”
11. Authors should consider discussing about available reports of HLH and subsequent lymphoproliferative disorders (or Hodgkin lymphoma) in the literature. Presumably, EBV was the driving factor for both but the precedence of HLH in this case has to be noted and discussed.

We have added the following text:

“Our patient developed HLH as the first symptom of HL. Although HL-associated HLH is rare, a previous retrospective study showed that EBV was highly detected in patients with HL-associated HLH (14). Patients with HIV-associated HL, in whom HLH is more common, also exhibit a high prevalence of EBV. These findings suggest that patients with HL-associated HLH might have an unclear underlying immune disturbance for EBV. Our case indicates that clinicians should perform BM biopsies to check for PBMHL in patients with 1) pancytopenia, 2) low CD4+ T cell counts (or lymphocytopenia), and 3) EBV-DNA positivity.”

12. Discussion, Lines 50-52: Third reason can be removed as there are phase 3 clinical trials reporting BV with AVD (ECHELON trial results, NEJM 2018) and hence in-vitro data are irrelevant at this point.

At the time of submission, only a phase I trial in a blood journal was available. We have changed Reference #10 as the reviewer indicated.

13. Conclusion of Abstract should be modified to state and describe the outcome in this case and not provide therapy recommendations based on a single case, particularly without addressing comment number 10.

We have revised the text as follows:

“Based on this patient’s progress, we propose that combined therapy with BV and AVD could be an alternative therapeutic option for PBMHL.”