Peer Review File

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Reviewer A

This is the first revision of an interesting case presentation. I would like to give my comments with the hope that these will be useful for the authors.

Comments:
1. page 3 line 73 the sentence « the disease was relapsed repeatedly » should be grammatically corrected.
Reply 1: We have modified the sentence as advised (see page 4 line 71 to 72).
Changes in the text: page 4 line 71.

2. page 4 line 96: the patient received front-line chemotherapy, guidelines recommend radiotherapy. You didn't discuss this possibility for this patient especially on the only non responding to PAD nasal mass.
Reply 2: Radiotherapy is recommended as the fist-line treatment for located tumor. The patient discussed in this article has a disseminated disease, especially mainly involving the lungs. In view of the difficulty in irradicating all the lesions at the same time and possibility of radiation pneumonia, we didn't choose the radiotherapy for the young patient.

3. page 4 line 97: the patient had PTI with platelets<50G/L. What dose of chemotherapy did you use for PAD, VRD and CHOP? Did you have to use reduced dose? Moreover, you used miniCHOP instead of CHOP for a patient of 23years-old with a very bad prognosis. What were the considerations leading to this reduced dose?
Reply 3:The dose of chemotherapy have been added in the manuscript. The miniCHOP for this young patient based on the following considerations: Firstly, the patient has a history of ITP, platelet counts were below 50×10^9/L. There would be a higher bleeding risk after standard CHOP therapy compared with miniCHOP. Secondly, the patient has severe skin and soft tissue infections in his right leg, when he accepted the first miniCHOP therapy. To avoid the deterioration of infections, we reduce the dose of CHOP. Finally, although the patient just accepted the miniCHOP therapy, he still suffered from severe lung infection after his first-course miniCHOP. Therefore, in view of above reasons, we used miniCHOP instead of CHOP for the young patient.
Changes in the text: page 5 line 97 to 105, page 6 line 120 to 121.

4. page 6 line 149. Your references for guidelines of treatment are based on case reports (references 18 and 19). references for treatment should contain international

guidelines publications or expert recommendations.
Reply 4: We have replaced the previous references (reference 18 and 19) with new references and guidelines as advised.
Changes in the text: page 8 line 164 to 167, page 12 line 286 to 294.

5. page 6 line 159-161: The references used to refer to « recent studies » are not studies but case reports. References should be refreshed to refer to the actual clinical studies.
Reply 5: Due to the low incidence of extramedullary plasmacytoma, there is currently a lack of studies on a large sample of bortezomib-based chemotherapy regimens for the treatment of extramedullary plasmacytoma. Therefore, « recent studies » mentioned in the article was not precise, and we have modified it to «several reports».
Changes in the text: page 8 line 174.

6. page 6 line 161: 3 6 of 7". the sentence start with a number therefore the first number should be in letters.
Reply 6: Thank you for pointing out this error, we have corrected it in the revised manuscript.
Changes in the text: page 8 line 176.

7. page 7 line 173. « some studies », which studies? you did not put any reference regarding those studies. The potential effect of epigenetics drugs is the main item of this case report and should be argued in the discussion.
For example: Dimopoulos published a review in 2014 int Blood Cancer Journal « The role of epigenetics in the biology of multiple myeloma »
Reply 7: We have supplemented the relevant literature on the role of epigenetic mechanisms in myeloma, and discussed the potential effect of decitabine and chidamide in the treatment of myeloma.
Changes in the text: page 9 line 188 to 195.

8. Page 7 line 181 the first word should be a W instead of a w.
Reply 8: We have corrected this error in the revised manuscript.
Changes in the text: page 10 line 202.

9. References: you did not put any reference after 2015, more recent references should be added: for examples international guidelines for treatment avec been published since
Reply 9: We have added several references (reference 13/14/23/24/30/31/32/33) published after 2015 in the manuscript.
Changes in the text: page 12 line 261 to 266, page 12 line 289 to 294, page 13 line 307 to 316.

Reviewer B

Cheng et al report a case of multiple extramedullary plasmacytomas in a 23 y/o male with ITP, involving the nasopharynx and respiratory tract. The authors do a literature review on this presentation, and discuss epigenetic therapy as a potential treatment option. This is an interesting case, and the case report would be strengthened if the following items are addressed:
- there are multiple grammar/spelling errors that need to be corrected.
Reply 1: We have corrected the grammar/spelling errors in the manuscript.
Changes in the text: page 4 line 71, page 8 line 176, page 10 line 202.

- there are too many figures. Would cut back to one or two figures and keep the one table.
Reply 2: Thank you for your kind suggestions. We considered that these pictures in the article would help peers to understand the patient's diagnosis and treatment in detail. We hope that we would be allowed to keep the pictures in the article.

- What was the heavy chain component of the EMP? Was it IgG, IgA or IgM?
Reply 3: As we have depicted in the article, both blood and urine immunofixation electrophoresis were negative, serum free light chain was normal. Thus, none of M components were detected in this case.

- Were serum immunoglobulin values obtained?
Reply 4: The serum immunoglobulin values have been added in case history of the patient.
Changes in the text:
Changes in the text: page 4 line 78 to 79.

- Was FISH performed, or just standard karyotype?
Reply 5: We performed two bone marrow aspirations and biopsies in this case, but no bone marrow involvement has been found. We didn’t observe any karyotypic abnormality by karyotyping. FISH was not performed in the bone marrow sample.

- Would discuss further the role of EBV in plasma cell disorders, and what is in the literature. Does EBV drive the extramedullary plasmacytoma?
Reply 6: We further discussed the role of epigenetic mechanisms in EMP as advised. Whereas, There is not enough understanding of the role of EBV in EMP, more researches are needed to explore the question about how EBV drive the extramedullary plasmacytoma.
Changes in the text: page 7 line 148 to 152.

- It could be argued that multiple extramedullary plasmacytomas are diagnostic for multiple myeloma, in contradistinction to a single extramedullary plasmacytoma. Please clarify.
Reply 7: In extramedullary plasmacytoma there are no clinical features of plasma cell

myeloma. The patient we reported in the article didn't have any symptoms of multiple myeloma such as anemia, hypercalcemia, renal insufficiency, bone lesions. Meanwhile, M components was not detected in blood and nurine samples and serum free light chain was normal. Thus, this case didn't meet the diagnosis of multiple myeloma.

- How do you know the tumors were not plasmablastic lymphoma? Please discuss why plasmablastic lymphoma was not the diagnosis. Also, the pulmonary nodules are worrisome for LyG - please explain why EBV driven lymphomatous granulomatosis (LyG) was not present. Please comment on whether PET imaging showed any lymphadenopathy or splenomegaly that would be indicative of lymphoma.
Reply 8: 1. Plasmablastic lymphoma is a very aggressive lymphoma that have a CD20-negative plasmacytic phenotype, high Ki67 index (> 90%), and are positive for plasma cell markers, such as CD38, CD138, and MUM1 with light chain restriction. In general, Ki67 index is significantly higher in PBL than in EMP. The patient reported in our article had a low Ki67 index (20%+) and relatively indolent course, which was not so aggressive as PBL, thus we diagnosed the case as EMP. 2. The EBV-positive B cells usually express CD20 in LyG. Whereas, tumor cells from biopsy specimens in our case were negative for CD20. We consider that there was insufficient evidence for the diagnosis of LyG in this patient. 3. Various imaging examinations including ultrasound, CT, MRI and PET/CT did not find any lymphadenopathy or splenomegaly in this patient.

- Please clarify - was there involvement in the right hip?
Reply 9: As we can see in picture 4, PET/CT revealed a nodule with high metabolism on the right hip, but we did not perform a pathological biopsy on this nodule. According to the changes before and after treatment, we thought that it was the involvement of the systematic disease.
Changes in the text: page 10 line 203.

- Why was CHOP dose reduced? Why was rituximab not added? What were the B-cell and T-cell markers of the plasmacytoma? (i.e. what was CD10, CD20, etc)
Reply 10: 1. The miniCHOP for this young patient is based on the following considerations: Firstly, the patient has a history of ITP, platelet counts were below 50×10^9/L. There would be a higher bleeding risk after standard CHOP therapy compared with miniCHOP. Secondly, the patient has severe skin and soft tissue infections in his right leg, when he accepted the first miniCHOP therapy. To avoid the deterioration of infecions, we reduce the dose of CHOP. Finally, although the patient just accepted the miniCHOP therapy, he still suffered from severe lung infection after his first-course miniCHOP. Therefore, in view of above reasons, we used miniCHOP instead of CHOP for the young patient. 2. Tumor cell in our case did not express CD20, thus rituximab was not added into the chemotherapy. 3. Tumor cells in the patient were phenotypically characterized by CD20(-), CD56(-), CD3(-), CD10(-), bcl-6(-), CD99(+), CD79a(+), CD38(+), CD138(-), CD5(-), MUM-1(+), Kappa(-),

Lambda(+), ki-67(20%+), and fluorescence in situ hybridization(FISH) suggested EBV-EBER (+).

- Please discuss mechanism of action of decitabine and chidamide, and how these works on epigenetics.
- Please discuss what is known about epigenetic drivers of extramedullary plasmacytomas as well as lymphomas. What is in the literature? What epigenetic pathways are involved? What data are available?

Reply 11-12: We have supplemented the relevant literature on the role of epigenetic mechanisms in myeloma, and discussed the potential effect of decitabine and chidamide in the treatment of myeloma. Because the extramedullary plasmacytomas is a rare disease, there is a lack of research on the epigenetic mechanisms involving the occurrence, development and treatment of extramedullary plasmacytomas. The combination of decitabine and chidamide in the treatment of the patient with multiple extramedullary plasmacytoma referred to the latest research on epigenetic therapy in multiple myeloma.

Changes in the text: page 9 line 188 to 195.

- Did your patient have any underlying immunocompromising conditions? Such as HIV, rheumatoid arthritis, post-solid organ transplant, immunosuppressive therapy, etc.? Any suspicion for a congenital immunodeficiency disorder given his young age? Did he have any recurrent infections? Perhaps his ITP is a manifestation of underlying immune dysfunction?

Reply 13: The patient only has a medical history of ITP and accepted the treatment of glucocorticoid and IV immunoglobulin, prolonged use of glucocorticoids may cause immune dysfunction in this patient.

- Please spell out what "MP" stands for (melphalan/prednisone)

Reply 14: "MP" in the manuscript stands for melphalan and prednisone just as showed in the table 1. We also give an explanation in the article.

Changes in the text: page 8, line 173.

- Please further discuss what happened to the patient. How many cycles of decitabine/chidamide did he receive? How long did these treatments work for? How did he die? What was his survival from time of diagnosis to death?

Reply 15: The patient received a total of 9 courses treatment of decitabine/chidamide until chest CT revealed disease progression in September 2019, and achieved disease progression-free survival for up to 8 months. The patient quitted therapy due to personal family conditions and was lost to follow-up at the beginning of this year.

Changes in the text: page 6, line 129 to 130.