Peer Review File

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Reviewer A

The paper entitled: ALK-positive anaplastic large-cell lymphoma with primary bone involvement: A case report is interesting case report. This case is well written and original

Reply: We are pleased to receive the approval of the reviewer. In the following work, we will further study relevant cases in order to better summarize treatment experience.

Reviewer B

very interesting case and well written report

Reply: We thank the reviewer for the recognition, which will motivate us for future work.

Reviewer C

The authors report a case of primary bone ALK positive ALCL. But diagnostic approach is quite insufficiency. The reviewer can't recommend this manuscript for publication because of immature presentations for diagnosis. Some of the important issues which need to be addressed are as follows.

1. With pathological findings presented in the manuscript, ALCL is not clearly diagnosed. Authors should present the results of other T cell markers and clonal T cell receptor rearrangement test. ALK gene rearrangement was often observed in some cancers other than lymphoma and CD30 expression could be positive with ALK positive cancer such as lung cancer.

Reply 1: We fully agree with and thank the reviewer for the comments and suggestions. As is known to all, the aberrant loss of pan T-cell antigens is characteristic of ALCL, but nearly all have a clonal T cell receptor (TCR) gene rearrangement. By immunohistochemical analysis testing, we found that CD25 was positive, whereas

CD43 and CD34 were negative in the patient's vertebral biopsy specimen. In order to better clarify the diagnosis, we strive to persuade the patient to complete the test of clonal TCR rearrangement. Unfortunately, the patient ultimately refused. It should be noted that CD30 may be positive in ALK positive cancer such as lung cancer. The patient came to the hospital without any pulmonary symptoms. The first positron emission tomography-computed tomography (PET-CT) examination in a local hospital showed no abnormal metabolism in the patient's bilateral lungs. At the same time, the levels of carcinoembryonic antigen, glycan antigen 125, neuron specific enolase, and squamous cell carcinoma antigen were detected within normal ranges in the patient's peripheral blood. Based on the various examination results, the patient was diagnosed as ALK-positive anaplastic large-cell lymphoma.

Changes in the text: see Page 4, line 76-84, and Page 5, line 96-99

2. Authors don't present image findings at diagnosis such as PET-CT as the evidence of primary bone lymphoma. Not only MIP image, coronal image of PET-CT should be also presented to show increased uptake of FDG with bone cortex not bone marrow compatible with bone lymphoma.

Reply 2: We thank the reviewer for the comments and suggestions. The patient's first PET-CT examination was completed at the local hospital. It is a pity that we did not obtain the electronic version of the PET-CT image. In order to better describe the case, we had described the results of PET-CT in text.

Changes in the text: see Page 4, line 76-84

3. Authors did not consider the possibility of solid cancers with unknown primary site. This case showed multiple bone lesions. In general, multiple lesions suggest metastasis rather than primary lesion. Besides, bone metastasis could be first manifestation in some cases with adenocarcinoma of unknown primary site such as prostate cancer and lung cancer.
Tumor markers such as PSA and IHC staining of TTF-1 and/or CK7 should be examined.

Reply 3: We sincerely appreciate the reviewer's criticism. The differential diagnoses of ALCL originating primarily in the bone include metastatic tumor, sarcoma, melanoma, osteomyelitis, and granulocytic sarcoma. Apart from morphology,

immunohistochemical stains will help to differentiate ALCL from other entities. The level of prostate specific antigen was detected within normal ranges in the patient's peripheral blood. We are afraid IHC staining of TTF-1 and CK7 were not examined. The diagnosis of ALK-positive anaplastic large-cell lymphoma with primary bone involvement was cautious and based on the results of various examinations.

Changes in the text: see Page 4-6, line 76-109

Reviewer D

I would like to congratulate the authors on presenting an interesting and rare case of ALK positive primary bone ALCL for the readers. The case, management and discussion are appropriately discussed however, there are edits required for better readability and flow of the article. Specific comments include:

1. Overall, article reads well however there are several minor grammatical errors that need attention. Would recommend using a grammar checker with Microsoft word or something like Grammarly (I do not have any COI with Grammarly) or other editing of their choice.

Reply 1: We thank the reviewer for the comments and suggestions. We used Grammarly to check the text and made corresponding modifications.

2. In the abstract, authors conclude that clinical significance of ALK expression in ALCL is not clear. There is no mention of this in background or case description to conclude this in the abstract section. Hence, they will need to change their conclusions.

Reply 2: Thank you for the suggestions. We apologize for the confusion generated by the previous version of the manuscript and sincerely hope that our logic is now easier to follow with this new version.

Changes in the text: see Page 2, line 39-42

3. Line 53 needs a reference.

Reply 3: We sincerely appreciate the reviewer’s criticism. We have supplemented our reference with the regarding paper (ref 1) and adjusted the text order.

Changes in the text: see Page 3, line 54

4. Line 55 needs a reference if available.

Reply 4: Thank you for the suggestions. We have supplemented our reference with the regarding paper (ref 1 and 2).

Changes in the text: see Page 3, line 55

5. Under case presentation, the second sentence is testing of HBsAg. Wanted to clarify if this is routine practice for all patients hospitalized in China or was this done once the pt was diagnosed with a malignancy to start therapy as part of pre-chemo evaluation. If it is the latter, that sentence will need to be moved further along during case presentation.

Reply 5: We fully agree with and thank the reviewer for the comments and suggestions. The test of HBsAg was as part of pre-chemo evaluation with a malignancy to start therapy. For better explanation, we have adjusted the text order.

Changes in the text: see Page 4, line 84-86

6. Would attempt to make case presentation a bit more concise to avoid redundancies.

Reply 6: Thank you for the suggestions. Considering the rarity of the case, we hoped to fully describe the course of the patient's treatment and provide a complete treatment experience. At the same time, we sincerely hope to make the case presentation relatively concise.

Changes in the text: see Page 4-7, line 71-136

7. Initial part of discussion has overlaps with introduction which should be edited.

Reply 7: We fully agree with and thank the reviewer for the comments and suggestions. For better explanation, we have modified the text.

Changes in the text: see Page 3, line 51-68 and Page 7-8, line 143-163

8. Would encourage authors to include a paragraph on how their management is similar

or different compared to other case reports of primary bone ALCL.

Reply 8: We appreciate the reviewer's suggestions. In our case, the patient was initially misdiagnosed as multiple myeloma. Vertebral body biopsy helped us to make the correct diagnosis. In contrast to other cases, the patient was treated not only with chemotherapy and local radiotherapy but also denosumab treatment. Meanwhile, sufficient stem cells were collected as a possible consolidation of autologous stem cell transplantation. For better explanation, we have modified the text.

Changes in the text: Page 10, line 219-224

9. Need to better delineate why their case is unique compared to the other reported cases. Perhaps one way to highlight it is that this condition may be misdiagnosed and hence require appropriate evaluation in the upfront setting.

Reply 9: Thank you for the suggestions. In our case, the patient was initially misdiagnosed as multiple myeloma. Vertebral body biopsy helped us to make the correct diagnosis. In contrast to other cases, the patient was treated not only with chemotherapy and local radiotherapy but also denosumab treatment. Meanwhile, sufficient stem cells were collected as a possible consolidation of autologous stem cell transplantation. Fortunately, the patient's bone pain has been controlled and he is generally in good condition. For better explanation, we have modified the text.

Changes in the text: Page 10, line 219-224

10. Consider adding other references including these case reports which are like yours:
a. PMID: 23605839 (Nayak et al)
b. PMID: 36993828 (Tutaeva et al)
c. PMID: 25738071 (Gajendra et al)
d. PMID: 27729639 (Kim et al)

Reply 10: We sincerely appreciate the reviewer's criticism. We have supplemented our reference with the regarding paper (ref 7,8, and 10). we sincerely hope to make the case presentation relatively better.

Changes in the text: Page 15, line 315-325