Peer Review File

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Reviewer A

1. Hemophilus syndrome: this is incorrect

Response：Thank you very much for reviewer's careful examination. We felt sorry for our mistake and changed the hemophilus to hemophagocytic in the revised manuscript.

2. GGO: please indicate the first time its meaning

Response: We appreciate the reviewer for this insightful comment. We added the GGO's meaning when it first appeared in the revised manuscript.

3. Histology picture: The HE legend does not correlate with the picture. The picture should be better. The IHC pics are correct.

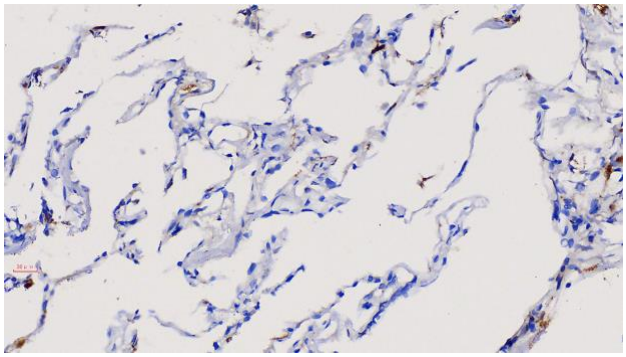
Response: Thank you for the reviewer's reminding. We consulted the pathologist again and revised the HE legend. Furthermore, we adjusted the picture of Figure 2A to make it more clearer and added the scale bar on each picture.

Reviewer B

Major point:

You described that the tumor cells include MPO-positive cells? Were the MPO-positive cells intermingled inflammatory cells? MPO-positive cells are granulocytes, not lymphocytes, and IVLBCL is a tumor of B-lymphocytes. If the tumor cells did express MPO, this case is not pure IVLBCL. In the present case, flowcytometry showed light chain restriction, and large cells showed CD20-positive, right? Presumably, mPSL was administered initially, which could increase in granulocytic series, often with left shift. Please confirm the MPO-positive cells were tumor cells. If the tumor cells were all CD20 positive cells, I agree the present case was IVLBCL.

Response: We appreciate the reviewer for the valuable comment. We did the IHC of MPO marker once more with the help of the pathologist and it showed that all the tumor cells were MPO negative cells. We added the picture as follows and revised the manuscript. We felt sorry for the mistake and thank you very much for the reviewer's professional suggestion.



IHC stain showing MPO-negative tumor cells (original magnification ×400)

Minor point

1. Does the sentence of line 39 in Introduction "Clinical symptoms occur-----" mean that there may be various symptoms depending on the site which tumor involves? Please explain clearly.

Response: Thank you for the reviewer's question. "Clinical symptoms occur-----"mean that when lymphoma cells proliferate within the lumina of the small vessels, there will be some clinical manifestations. The reviewer's understanding is completely correct. The blood vessels involved in different organs have different manifestations. So we rearranged the sentence in the revised manuscript to make it easier to understand.

2. Line 43 "findings are often nonspecific." It would be better to explain specifically and with a little more detail and put an emphasis on the lung-specific problems; the most common pattern of CT findings of IVLBCL is bilateral GGO. The differential diagnoses of pulmonary GGO (pure or mixed) include many etiologies, not only malignant tumor (malignant lymphoma, early lung cancer, etc.) but also infection and interstitial inflammatory diseases. Further, collecting enough samples with good quality to make the definitive diagnosis is challenging using current TBLB, I think.

Response: We appreciate the reviewer for this insightful comment. According to the reviewer's suggestion, we added "The most common pattern of CT findings of IVLBCL is bilateral ground glass opacities (GGO). However, the differential diagnoses of pulmonary GGO include many etiologies, not only malignant tumor but also infection and interstitial inflammatory diseases." to explain more detail about CT imaging of IVLBCL involving lung.

3. Line 56. Please identify the nodules or GGO using arrows or arrowheads.

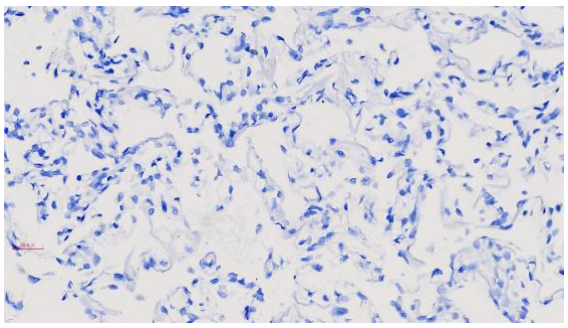
Response: We admire the reviewer's rigorous scientific attitude. We added the red arrow and oval on the figure 1 to identify the nodules and GGO. We also added the explanation in the legend.

4. Line 60 "immunosuppressant" means steroid? Does the drug is oral or external? Please describe in detail. This description is important because if the

dug was oral, it suggests the patient was an immunocompromised host and the possibility of immunodeficiency-related lymphoma.
Response: Thank you very much for the reviewer's professional suggestions. The patient accepted a combination of oral and external steroids for many years. We added the sentence "a combination of oral and external glucocorticoids" in the revised manuscript. Furthermore, we agree with the reviewer that the patient may have immunodeficiency-related lymphoma.

5. In the clinical data, it would be better to include clinical test items.
1) COVID examination because of current status.
2)LDH, sIL-2R level.
3) Ferritin
4) eosinophil count in peripheral blood
5) EBV -associated item
Response： We appreciate the reviewer for this insightful comment. According the reviewer's suggestion, we improved the relevant clinical data listed in the above question. However, we had no sIL-2R test item in our hospital. We cannot know the sIL-2R level of the patient.

6. In the histopathological description, it would be better to add or amend some points below.
1) How was EBER-ISH? This is important if the patient was immunocompromised.
Response: Thank you for the reviewer's professional question. We did the IHC of EBER marker with the help of the pathologist and it showed that EBER was negative. The patient was positive for EBV-CA and NA IgG antibodies which illustrating that he had a history of EB virus infection. However, he was negative for EBER which suggesting that EB virus infection was not relative with IVLBCL on the patient. We added the picture as follows:



IHC+ ISH showing EBER-negative tumor cells (magnification×400)

2) Line 80, 81. The positivity of CD20, PAX 5, CD19, and negativity of CD3, CK is lineage decisive, and CD10, BCL6, MUM1(please add MUM-1) status mean the GCB or non-GCB phenotype of B-cell lymphoma. It would be better to describe separately. IVLBCL is the almost non-GCB phenotype.
Response: We admire the reviewer's professional attitude. We adjusted the order of

CD markers to identify the lineage of lymphoma. Furthermore, we added the histochemistry of MUM1 marker and it was negative for MUM1. According to the decision tree proposed by Hans et al., it was regarded as the GCB phenotype from the result of CD10(-) BCL6(+) MUM1(-)[1]. However, most of IVLBCL are non-GCB phenotype as the reviewer's mentioned, which is not consistent with the present case seemingly. We further studied some articles and found that a minority of patients were GCB phenotype [2]. We discussed the pointed in the revised manuscript.

1. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO, Chan WC. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004 Jan 1;103(1):275-82.
2. Murase T, Yamaguchi M, Suzuki R, Okamoto M, Sato Y, Tamaru J, Kojima M, Miura I, Mori N, Yoshino T, Nakamura S. Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood. 2007 Jan 15;109(2):478-85.

3) In the bone marrow, were the tumor cells in the vessels? Or did they form nodules?

Response: Thank you for your critical comments. This patient had a bone biopsy, but most of the specimens were fat vacuoles, and there were few nucleated cells that could be recognized. Therefore, it was difficult for us to determine whether the tumor cells were in blood vessels or not through the result of bone marrow.

4) Line 86. What is FS intensity?

Response: We appreciate the reviewer for this insightful comment. FS means Forward Scatter. In fact, we missed the letter "C", which should be FSC. The signal intensity of FSC was proportional to cell size. We changed the "FS intensity" to the "forward scatter signal" for better understanding.

5) Which did the tumor cells express □ or □?

Response: We felt sorry that the question cannot be shown completely. "**Which did the tumor cells express □ or □?**" We cannot understand the meaning.

6) Haemophilus syndrome? Bacterial infection? You mean "hemophagocytic syndrome (HPS)"? IVLBCL often accompanies HPS.

Response: Thank you very much for reviewer's careful examination. We changed the hemophilus to hemophagocytic in the revised manuscript. The patient met the diagnostic criteria for HPS. He had fever, splenomegaly and hemosytopenia. Hemophagocytosis was found in bone marrow and ferritin was more than 500ug/l.

7) In flowcytometric data, CD11c, 103 are unnecessary if the tumor was B-cell lymphoma.

Response: Thank you very much for the reviewer's professional suggestions. We deleted the CD11c,103 in the revised manuscript according the suggestion.

8) In the bone marrow, did the tumor cells express the same light chain as in the lung?

Response: Thank you very much for the reviewer's careful examination. The tumor cell express the kappa light chain which was same as in the lung. We added it in the revised manuscript.

9) The patient developed pancytopenia, and HPS probably occurred in the bone marrow. How were the cellularity and three hematopoietic series (granulocytic, erythroid, megakaryocytic series) in the bone marrow?

Response: Thank you for the reviewer's useful suggestion. Bone marrow showed that bone marrow hyperplasia was active and the ratio of grain to red decreased (1.09:1). The granulocytic hyperplasia was active with left nuclear shift. The erythroid hyperplasia was active with karyolobism. The megakaryocytic hyperplasia was active, totally with 34 megakaryocytes. It also showed 10.5% abnormal lymphocytes. They were large and irregular with haemophilus cells visible. We added the above information in the revised manuscript.

7. In the discussion, I think the general explanation of IVLBCL is too long (paragraphs 1 and 2). Please focus on the specific point of the present case.

Response: Thank you for the reviewer's critical comments. According your suggestion, we deleted a part of the content about the general explanation of IVLBCL and added the content about diagnosis value of diffuse lung diseases by transbronchial lung cryobiopsy.

8. In discussion, Line 100, you cited the paper numbered (5). Is that correct?

Response: Thank you for the reviewer's professional question. According to the 7th question, we deleted this sentence including 5th citation, and focused on the specific point of the present case.

9. Line 118. On CT findings, did the diffuse GGO initially and later nodules and septal thickening occur?

Response: Thank you for the reviewer's professional question. However, we did not see the diffuse GGO initially and later nodules and septal thickening occurring on CT finding. It might be related with the shorter interval between the first and second chest CT examination time.

10. The picture of Figure 2A should be presented with a high-power field so that readers can see the tumor cells precisely. Moreover, each picture should have a scale bar.

Response: Thank you for the reviewer's suggestion. We adjusted the Figure 2A to make it more clearly and each picture had been added the scale bar.