Author’s response to reviews

Title: De novo acute lymphoblastic leukemia-like disease of high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements: a case report and literature review

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Author’s response to reviews:

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Professor Dan Jones, M.D., Ph.D.
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Re: De novo acute leukemia-like disease of high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements: a case report and literature review (CPAT-D-17-00019R1)
Dear Dr. Jones,

We greatly thank you and the reviewers for suggestive comments on our manuscript.

We carefully checked the reviewers’ comments and added the description about the differentiation stage of acute leukemia-like disease harboring MYC and BCL2 and/or BCL6 rearrangements, which we call ‘AL-HGBL’. One more paper was cited in this description (re. no. 40). Concerning the point of our manuscript, there remains the issue between the Reviewer #1 and us. Although the current WHO classification defined high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBL) as a mature (terminal deoxynucleotidyl transferase (TdT)-negative) B-cell lymphoma in spite of the cell morphology (ref. no. 3), this situation is likely based on the process of establishing this disease entity. Among Burkitt lymphoma-like B-cell lymphomas harboring MYC rearrangement, around 30% of the cases simultaneously have BCL2 rearrangement and showed a poor prognosis (Aukema SM, et al. Blood 2011; 117: 2319.; Macpherson N, et al. J Clin Oncol 1999; 17: 1558.). Such cases had been called ‘double-hit lymphoma’ in the 4th edition of the WHO classification (2008) and were now defined as ‘HGBL’ in the revised one (ref. no. 3). Thus, most HGBL cases are thought to be Burkitt-like lymphoma or diffuse large B-cell lymphoma. On the other hand, several AL-HGBL have been reported incidentally. Among them, some cases were considered to be precursor B-cell acute leukemia because the leukemic cells were positive for TdT and failed to be detected their surface immunoglobulins. As described in Background section, however, MYC rearrangement should almost occur at peripheral germinal center (GC)-B-cell stage (ref. n.1; Goossens T, et al. Proc Natl Acad Sci USA. 1998; 95: 2463.). Because the disruption of MYC has a potential to induce reversion of the host cells (ref. no. 38), AL-HGBL cells also originate from GC B cells and might revert back to the immature stage. Therefore, we believe that TdT-positive AL-HGBL can exist and is same as TdT-negative AL-HGBL.

I look forward to receiving your reply and hope that this manuscript is appropriate for publishing in “BMC Clinical Pathology”.

Sincerely Yours,

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Response to the reviewer’s comments

To the Reviewer #1:

We greatly thank the Reviewer #1 for suggestive comments that have helped us to improve our manuscript. According to the reviewer’s comment, we almost revised this manuscript. However, we have an important issue to discuss between the Reviewer #1 and us.

The major point is about the differentiation stage of acute leukemia-like disease harboring MYC and BCL2 and/or BCL6 rearrangements, which we called ‘AL-HGBL’. As mentioned by the Reviewer #1, the current WHO classification defined high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBL) as a mature B-cell lymphoma in spite of the cell morphology, while this classification has not yet defined alteration of lymphoma cells in the differentiation stage. As shown in the recent report (ref. no. 33), HGBL can present with features suggestive of immaturity such as the expression of terminal deoxynucleotidyl transferase (TdT). As described in Background section, the acquisition of t(14;18)(q32;q21) and the 8q24/MYC translocation is considered to occur in precursor-B-cell and germinal-center (GC)-B-cell stages, respectively. Hence, the lymphoma with both gene alterations should be recognized as a mature B-cell lymphoma, which has differentiated at least into the GC-B-cell stage. However, the MYC is known to play a crucial role in the generation of induced pluripotent stem cells and is reported to have a potential to induce reversion of hematopoietic cells (ref. no. 38). In addition, the acquisition of MYC rearrangement in follicular lymphoma (FL) is reported to induce the morphological change and the TdT expression in transformed FL cells (ref. no. 40). On the other hand, the expression levels of TdT gene is relatively increased in GC-B-type diffuse large B-cell lymphoma (Aizadeh AA, et al. Nature. 2000; 403:503.).

Taken together, AL-HGBL cells with immature B-cell phenotype may originally develop from GC-B cells, and can express additional molecules including TdT, which may be induced by the disruptions of MYC and other molecules. Although the TdT expression in HGBL fails to be acknowledged in the current WHO classification, we believe that some of HGBL cases especially showing blastoid morphology can exhibit an immature phenotype. Therefore, we should not exclude TdT-positive AL-HGBL cases in the literature review of this manuscript. We added the description in Background (P3, L15-16) and Discussion sections (P6, 21-24). As described in Literature review section, transformed FL cases had been excluded.
Response to minor points:

1. We added the information of TdT negativity in Abstract section (P2, L10).

2. We agree the reviewer’s comment and also understand that the lymphoblast-like tumor cells are mature B cells. We used the term ‘blastoid cells’ instead of the term ‘lymphoblast’ (P3, L29 and L34; P4, L3 and L16).

3. ‘AL-HGBL’ is clinically characterized as the acute onset disease with the initial manifestation of BM infiltration by blastoid cells but lacking tumor formation. We added the description in Background section (P3, L18-19).

To the Reviewer #2:

We greatly thank the Reviewer #2 for suggestive comments that have helped us to improve our manuscript.

Response to minor points:

1. We corrected the typing error (P3, L12).

2. We added the description about the method that we used to calculate MIB-1 index (P4, L14-15).

3. As shown in Figure 1, the patient presented no hepatosplenomegaly and had no mass lesion. FDG accumulation is mainly detected in bone marrow. Similar accumulation pattern was reported in B-cell acute lymphoblastic leukemia patients (Kato-Arimoto M, et al. Springerplus. 2015; 4:521.). Although primary bone marrow lymphoma is not ruled out, we first considered this case as acute leukemia rather than lymphoma based on the morphological assessment of the bone marrow.