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

We greatly thank you for suggestive comments on our manuscript. We carefully checked your comments and changed the title and the term “AL-HGBL” into “acute leukemia-like disease with MYC and BCL2 rearrangements (AL-DHL)”.

Nevertheless, I am concerned that the discussion points are still remained between you and us. Just to make things clear, we don’t describe that the expression of CD10 alone is the marker of germinal center B (GCB) cells. As mentioned by Hans and colleagues, GCB cells are supposed to express at least both CD10 and Bcl-6. However, many previous reports lack the description about the expression of Bcl-6. Although the present case failed to show the expression of TdT, we believed that GCB-derived lymphoma cells could express TdT because we had experienced a couple of cases with transformed follicular lymphoma, which showed the expression of TdT, CD10, Bcl-6 and surface IgM. Therefore, we discontinued to use the term “high grade B-cell lymphoma” in this review because the point of this manuscript is to introduce the remarkable character of AL-DHL. Furthermore, we shall emphasize that IGH-MYC rearrangement occurs almost always during class switch recombination (CSR) (Greisman and colleagues reported that about 95% of the rearrangement was developed during CSR. Blood 2012;120:2864). In mantle cell lymphoma and CLL without somatic hypermutation (SHM) in IGH variable region gene (IGHV), MYC rearrangement may occur at pre-GCB stage. However, more than half of CLL cases with MYC rearrangement were reported to have SHM in IGHV (Br J Haematol 2008;142:36), indicating that these CLL cells have passed GCs and are considered to acquire the rearrangement at GCB stage (reviewed by Fabbri and Dalla-Favera. Nature Rev Cancer 2016;16:145). The fusion between MYC and light chain gene is likely induced by the recombination-activating gene products because the receptor editing can also develop at the peripheral lymphoid tissues. However, the fusion between MYC and other genes is mainly induced by the activation-induced cytidine deaminase. Thus, we believe that the MYC rearrangement in double-hit B-cell lymphoma/leukemia usually occurs at GCB stage.

Although I understand that the current WHO classification dare not define the very rare and special condition, I would appreciate it very much if you could pick up these cases. I look forward to receiving your reply and hope that this revised manuscript is appropriate for publishing in “BMC Clinical Pathology”.

Sincerely Yours,

Yasushi Isobe, M.D., Ph.D.

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