April 29, 2020
Hiten RH Patel
Editor-in-Chief
World Journal of Clinical Oncology

Dear Editor,
Manuscript No: 54270
Title: Intravascular lymphoma with hypopituitarism: A case report

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *World Journal of Clinical Oncology*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers' suggestions. The revisions have been made using red font. The responses to all comments have been prepared and given below.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Response to Reviewer's Comment

Reviewer 1

1) Although IVL is B-cell in most cases, cases of T- and NK-cell intravascular lymphomas have also been described. The authors do not give the results of an immunohistochemical study, which is necessary, especially since the patient was treated with rituximab.

Immunohistochemical staining revealed positivity for the B-cell markers CD20 and CD79a in the absence of staining for T-cell markers. Based these findings, she was diagnosed with intravascular B-cell lymphoma. I have added the results of an immunohistochemical study (line 123-125).

2) The authors correctly emphasize the importance of random skin biopsy for the diagnosis of IVL. Histological examination of the bone marrow is performed. Trephine biopsy of bone marrow can also indicate IVL. Here, were there any histological signs of bone marrow lesion IVL?

Although bone marrow aspiration and biopsy often help the diagnosis of IVL, they revealed no evidence of tumor involvement in this case. I would like to mention it in 'Imaging examinations' section (line 115-116).

3) Biochemical data are lacking. Was there an increase in LDH? The value of LDH was 971 IU/L.

I have added some results of laboratory studies in 'Laboratory examinations' section (line 97-98).

4) Hemophagocytic lymphohistiocytosis (HLH) diagnosis requires a complex of diagnostic criteria [Filipovich and Chandrakasan, Hematol Oncol Clin N Am 29 (2015) 895–902]. Despite hemophagocytosis in bone marrow, fever and cytopenia in the patient, this is not enough to diagnose HLH.

She was diagnosed with HLH based on the criteria suggested by Up To Date. She met five of eight criteria of HLH (fever ≥38.5°C, splenomegaly, peripheral blood

cytopenia, hemophagocytosis in bone marrow, ferritin >500 ng/mL, elevated soluble IL-2 receptor alpha two standard deviations above age-adjusted laboratory-specific norms). I would like to mention it in 'Imaging examinations' section (line 116-119).

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Post TW, editor. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis#H636145411 (Accessed on April 30, 2020).

Reviewer 2

1) However, in the part of OUTCOME AND FOLLOW-UP, a brief supplement of the endocrinological condition may make the case more complete.

She has not shown any signs and symptoms associated with hypopituitarism for two years after treatment. She required only minimal hormone replacement therapy, 5mg/day of hydrocortisone. I would like to mention it in 'OUTCOME AND FOLLOW-UP' section (line 140-141).

2) In addition, in the part of CONCLUSION, "earlier disease stage" was mentioned in the manuscript, but what is defined as "earlier"? Is the definition of "earlier" based on the IVL severity or pituitary damage?

It is difficult to define "earlier disease stage" because of the limited number of cases of hypopituitarism associated with IVL. Although this case was stage IVB lymphoma (Ann Arbor staging system), chemotherapy was not too late for her because it was effective for the pituitary involvement. Further research is needed to assess this point. However, we did not change the phrase "earlier disease stage" because this phrase was worn out in the cited paper (Sawada et al.).