Author’s response to reviews

Title: First Case of Primary Intraocular Natural Killer T-cell Lymphoma

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Author’s response to reviews:

Dear Reviewers,

We thank a reviewer for pointing this out; this has been corrected. Also, we change and checked carefully for some errors in this article.

Reviewer #1: This is an interesting case report of a rare, possibly unique entity that is of interest to clinicians performing molecular diagnostics on vitreous specimens. It expands the knowledge base of intraocular lymphoma.

The narrative structure is straightforward, but not well written, due to language difficulties. This sentence is not comprehensible: "...a severe vitreous opacity with a small degree of cell infiltration was found....Retinitis...was unremarkable, with no evidence of vascular leakage or exudate in the retina caused by the vitreous opacity." Does this mean that there was vitreous haze out of proportion to cellularity? That there were no visible retinal lesions? That an angiogram was done that did not show vascular leakage? Why is this not referenced to photographs?

I would interpret Figure 1 a-c as showing both lesions and vascular leakage.

Response;

We thank the reviewer for the detailed comments. Indeed, as the reviewer has quoted, there was only minor vasculitis in this case, although there was some leakage of the retinal vessels. We have added an arrow to the figure to indicate visible leakage. Our reference to cell infiltration was a description of the cells in the vitreous cavity, which in this patient were smaller in size and
shape than those usually seen in patients with other types of uveitis, such as sarcoidosis. Finally, while we were unable to observe any retinal lesions in the first examination due to the severe vitreous opacity, during the operation, retinal lesions became visible over the entire retinal field. We have revised the “case presentation” section to clarify these details.

Other examples of poor word choice:

* "multiple disease lesions resembling lymphomas were found in the retina"

Response;

We appreciate the reviewer’s comments. We would like to revise this passage to read “multiple white or cream-colored lesions”.

* "dry-and-wet type vitreous specimens"

Response;

We are grateful for the reviewer’s comments. We would like to revise this passage to read “vitreous specimens were collected with or without BSS perfusion.”

* Which infections were tested by PCR? Please reference your previous published protocol.

Response;

We thank the reviewer for the question. We have added suitable references to the text.

* "histological examination of the retina indicated tumor was malignant". Malignant refers to clinical behavior. Was a retinal biopsy taken? It is not mentioned in the case report.

Response;

We appreciate the question. Yes, we performed a retinal biopsy. We would like to add the following sentence to clarify this: “A tentative diagnosis of primary intraocular lymphoma was made. Vitreous collection was then performed with 25-gauge microincision vitrectomy, and a retinal biopsy was taken.” The biopsy of the retinal lesion was approved by our IRB.

* The Background section states that NK-Tcell are CD3 negative (which is not correct I believe) but nonetheless there is no comment made later that this tumor was CD3 positive.

Response;
We are grateful for this comment on CD3 markers. In fact, NK T-cells are negative for CD3 surface markers, as the reviewer described, but positive for cytoplasmic CD3 epsilon markers. To clarify this point, we would like to revise the sentence the reviewer referred to, as follows: “Unlike large granular lymphocyte T-cells, this type of tumor is negative for CD3 surface markers, but positive for cytoplasmic CD3 epsilon and CD56 surface markers. Furthermore, the immunocytochemical analysis revealed that more than 90% of cells positive for CD2, CD56, CyCD3 and T-cell intracytoplasmic antigen (TIA) 1-1 were also positive for Ki67.”

In addition the gene rearrangement results are misstated: lack of TCR rearrangements doesn't mean that a cell is not a T lymphocyte, only that it is aberrant or that it does not have receptors.

Response;

We appreciate the reviewer’s careful attention. We would like to correct the sentence to read: “Moreover, the results of a gene rearrangement analysis were positive for the immunoglobulin heavy locus (IGH) and T-cell receptor (TCR) beta chains, especially the TCR beta chain, while the TCR alpha, beta, gamma and delta chains were all negative. This result indicated a clonal, abnormal chromosome.”

In summary the case has merit and uses excellent diagnostic techniques but is presented in a way that detracts from its meaning. Rewriting and rethinking the case will need to be done if revised. A larger image of the montage retina would be more interesting to clinicians than the PET scan. Please include OCT of the lesions if they are available.

Response;

We thank the reviewer for the positive comments and helpful suggestions. We have done our best to rewrite and rethink the case, and improve our presentation of our findings, in the revised version. Furthermore, as suggested, we have enlarged the fundus image in the figures and added OCT images of the initial stage of treatment.

Reviewer #2: This is a very interesting case that is nicely described.

I have only few comments or questions:

1.) Left eye of the patient was not affected at all?

Response;

We thank the reviewer for the question. Indeed, the left eye of the patient was not affected at all.

2.) Page 5, line 69: the authors report that a vitrectomy was performed.
Page 6, line 83: the authors mention a histological examination of the retina. Was a biopsy of the retina performed in addition?

Response;

We appreciate the reviewer’s comments. Yes, we performed a biopsy. We would like to add the following sentence to clarify this: “A biopsy of the retinal lesion was approved by our IRB.”

2.) I would be interested why the authors call this case a study and why they collected approval from review board and registered a study? In my opinion, all procedures that have been performed in this patient were necessary to establish diagnosis and to plan treatment. Thus, all procedures were in the context of regular medical care and not primarily for scientific research.

Response;

We are grateful for the reviewer’s comments. The policy of our university is to obtain the approval of our ethics committee when using patient samples from clinical examinations.

4.) Which kind of chemotherapy has to be done for such a tumor?

Response;

We appreciate the question. In response, we have added a description of the chemotherapy used in this case, as follows: “SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy”. The patient received 2 courses of SMILE chemotherapy. In the ocular tissue, we performed the vitreous injection of methotolexate twice a month until the start of chemotherapy and irradiation therapy.