Author’s response to reviews

Title: Bilateral granulomatous panuveitis in two patients with T-cell type of chronic active Epstein-Barr virus infection

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Author’s response to reviews:

Dr. Guangde Tu
BMC Ophthalmology
Editorial Office

Re: BOPH-D-18-00673

Bilateral granulomatous panuveitis in two patients with T-cell type of chronic active Epstein-Barr virus infection

Dear Dr. Tu,

Thank you very much for the valuable comments and the suggestions by the reviewer to improve our manuscript. Here, we revised the manuscript according to those comments, and we listed the point-by-point response as below. For convenience sake, we added the serial line number in the manuscript. By your comments, we believe that the revised manuscript may now be acceptable for publication in BMC Ophthalmology.

Sincerely,

Hiroshi Takase, M.D., Ph.D.

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Point-by-point response to the reviewer

Case 1:

1. Page 4, line 24: The lymphocytic fraction was isolated from the whole blood using antibody-conjugated magnetic beads. Please provide kit details.

Response: We have added the information of antibody-conjugated magnetic beads to the text (lines 57-61).

2. Page 4, line 27: The EBV-DNA load was determined to be 1.2 x 10^5 copies of DNA/μg in the whole blood. It should be 1.2 x 10^5 copies/μg DNA in the whole blood.

Response: We thank the reviewer for pointing out the grammatical problem. We corrected the sentence according to the suggestion (line 64).

Was EBV-DNA load determined by commercial kit or in-house qPCR? Please provide the manufacturer’s details or reference for the in-house qPCR.

Response: We examined EBV-DNA load by in-house qPCR according to the previous report. We have added that to the text (lines 61-63).

3. Page 4, line 31: EBV-DNA was detected in the CD4-positive T-cells in the peripheral blood. Please correct the “positive” spelling and what was the viral load in CD4-positive T-cells?

Response: We corrected the misspelling as indicated by the reviewer. We also added the viral load in CD4-positive cells to the text (lines 64-65).

4. Page 4, line 53: He was being treated with 0.1% betamethasone eye drops which was continued. Please mention the dose.

Response: Thank you very much for pointing out the missing information. We added the dose of the eye drop that was 4 times a day (line 75).
5. Page 5, line 1: Systemic immunochemotherapy consisting of steroids and cyclosporine was started for the CAEBV. Please provide complete details of the treatment. “Immunochemotherapy” is a single word. Please correct it.

Response: We thank again for pointing out the misspelling. We have added the details of the treatment to the text, and actually it was an immunetherapy, but not an immunetherapy. We therefore corrected the term in the text (line 77).

6. Page 5, line 7: His BCVA was decreased to 20/32, and slit-lamp ophthalmoscopy showed mutton-fat keratic precipitates (KPs) and 2+ cells in the anterior chamber and the anterior vitreous of both eyes (Figs. 1A and 1B). Please correct the sentence. Multiple “and”s in one sentence. Please re-write the sentence.

Use a comma (,) before any coordinating conjunction (and). In some places, it is missing.

Response: We thank the reviewer for suggesting re-writing the sentence. We corrected the sentence as “His BCVA was decreased to 20/32. Slit-lamp ophthalmoscopy showed mutton-fat keratic precipitates (KPs), 2+ cells in the anterior chamber, and 2+ cells in the anterior vitreous of both eyes (Figs. 1A and 1B).” (lines 80-82).

7. Page 5, line 12: The optic disc, fovea, and all of the retinal vessels of the right eye were covered with white infiltrates (Fig.1 C), and several white nodules were seen along the retinal veins and arteries of the left eye (Fig. 1 E). Please re-write the sentence.

Response: We re-wrote the sentence as “In the right eye, the optic disc, fovea, and all of the retinal vessels were covered with white infiltrates (Fig.1 C). In the left eye, several white nodules were seen along the retinal veins and arteries (Fig. 1 E).” (lines 82-85).

8. Page 5, line 31: The right anterior chamber was tapped and processed for multiplex PCR with a search for the presence of specific genomic sequences of all 8 types of human herpes viruses. Is it a commercial kit or in-house PCR? If it is a commercial kit, please provide the manufacturer’s details or if it is an in-house PCR, please provide the reference for the primers and methodology.

Response: We thank the reviewer for pointing out the missing information. The PCR was performed in our department, so we added the information regarding the methods and references for the primers and probes (lines 90-99).

9. Page 5, line 46: Cytokine analysis by enzyme-linked immunosorbent assay (ELISA) revealed that the interleukin (IL)-6 concentration was over 1000 pg/ml, whereas that of IL-10 was below the detectable level. Please provide ELISA kit details.
Response: We added the information regarding the ELISA kit we used, and re-wrote the sentences related to the cytokine measurement (lines 100-105).

10. Page 6, line 22: Although EBV-positive T-cells were not eradicated from the peripheral blood, the intraocular inflammation completely disappeared in 8 weeks. Please provide viral load details at 8 weeks.

Response: We have added the viral load to the text (lines 117-118).

11. Page 6, line 29: His last BCVA was 20/63 OD and 20/16 OS. Was it at 8 weeks after treatment? When was the last follow-up of this patient? At his last follow up, what was the viral load in AqH?

Response: Currently, the last follow up of this patient is 5 years after treatment. We changed the BCVA of this patient to that of last visit and re-wrote the sentences (lines 121-122). To our regret, we did not measure the viral load in AqH or vitreous after treatment, so we could not show add this information in the manuscript.

Case 2:

1. Page 7, line 12: EBV infection of the CD4-positive T-cells and their clonal proliferation were confirmed by the assays. Please mention the name of the assays and its references.

Response: We examined the clonality of EBV-infected cells by Southern blot analysis for EBV-terminal repeat in both cases. We have added the information and the reference to the text of case 1 (lines 65-66) and case 2 (line 139).

2. Please provide the details and/or references for PCR and ELISA.

Response: We used the same system for PCR and ELISA as we used for case 1. Therefore, we simply added “as describe in case 1” for PCR (lines 142-143), and added the company information of the ELISA kit (line 144).

3. Page 7, line 34: We treated the patients with 0.1% betamethasone eye drops… how many times a day and each time how many drops? Please provide complete treatment details.

Response: We added the information as “4 to 6 times a day, applying one drop each time” (lines 149-150).
4. Page 7, line 44: Although EBV-positive T-cells were not eradicated from the peripheral blood, the disease became inactive. Please provide the viral load details at last follow-up.

Response: We added the viral load to the text, and slightly modified the sentence (lines 154-156).

Discussion:

Page 9, line 5: there has been no studysd… Please correct it to “studies”

Response: We corrected the misspelling (line 186).

Please do crosscheck the manuscript for grammatical mistakes.

Response: We looked over the manuscript again in terms of grammatical mistakes and misspelling, and corrected the misspelling of “predonisalone” to “prednisolone” (line 112).