Author’s response to reviews

Title: Human herpesvirus-6 corneal endothelitis after intravitreal injection of ranibizumab

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RE: BOPH-D-18-00328

Human herpesvirus-6 corneal endothelitis after intravitreal injection of ranibizumab

Masahiro Onda; Yusuke Niimi; Kenji Ozawa; Ikumi Shiraki; Kiyofumi Mochizuki; Tetsuya Yamamoto; Sunao Sugita; Kyoko Ishida

Dear Editor-in-chief

Thank you for reviewing our manuscripts. We revised the manuscript according to the reviewers’ valuable comments. Below are the reviewers’ italicized comments followed by our responses.

Reviewer’s comment:
Your manuscript "Human herpesvirus-6 corneal endotheliitis after intravitreal injection of ranibizumab" (BOPH-D-18-00328) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Ophthalmology, once you have carried out some essential revisions suggested by our reviewers.

Reviewer reports:

Alejandro Fonollosa Calduch (Reviewer 1): This is an interesting case of a corneal endotheliitis due to HHV-6 after intravitreal injections of ranibizumab. I have a few comments:

In the title and throughout the paper "endotheliitis" is misspelled

Replay: (Title, Key-words, Abstract, and Text) We corrected the misspellings from "endotheliitis" to "endothelitis" in the title and throughout the paper.

1. In the abstract:
   - Please correct the OS VA value, you have written 2/20
   Replay: (Abstract, Line 38) We corrected the VA value to 2/200

   - the authors should provide the IOP, since it is relevant for the diagnosis
   Replay: (Abstract, Line 38) We added the information of IOP in the abstract.

   - According to the photographs I would say keratic precipitates are intermediate, not fine
   Replay: (Abstract, Line 39) We changed the word from "fine" to "intermediate".

2. Main text:
   - Again I think precipitates are intermediate
   Replay: (Main text, Line 79 and Figure Legends, Line 329) We changed the word from "fine" to "intermediate".

   - Line 69: it would be interesting to know the dose of steroids
   Replay: (Main text, Line from 71 to 73)
The steroid therapy started with prednisolone 20mg/day 2 years ago, gradually tapered, and had continued with 5mg/day for the last 6 months.

- Line 70: I would changed "has received..." for "had been receiving."

Replay: (Main text, Line 73 and Abstract, Line 35) We changed the sentences according to the reviewer’s comment.

- Line 90: the authors should explain why IgM antibodies were positive, that is to say acute infection, since as it is stated in the introduction, HHV-6 infection typically occurs during childhood.

Replay: (Main text, from Line 93 to 95) We miswrote the sentence and corrected it. Anti-HHV-6 IgG antibody was positive (40 times) and anti-HHV-6 IgM antibody was negative (<10 times) in blood samples. This means that the patient had prior infection of HHV-6.

The Discussion is too large; as it is recommended in the instructions for authors: "a brief summary of the clinical impact or potential implications of the case report" is enough; please make the discussion shorter.

Replay: (Discussion) To make the discussion shorter, we deleted and changed several sentences.

(Discussion, Line from 114 to 116) We deleted the sentence.

(Discussion, Line from 118 to 122) We changed the sentence shorter.

(Discussion, Line from 145 to 150) We changed the sentence shorter.

(Discussion, Line from 151 to 156) We deleted the sentence and the reference 31.

(Reference, from No.31 to No.36) We changed the reference numbers thereafter.

(Discussion, Line from 175 to 176) We changed the sentence shorter.

(Discussion, Line from 178 to 179) We deleted the sentence.

Yi Lu (Reviewer 2): 1. Though it was hard to tell the correlation between the intravitreal injection of ranibizumab and HHV-6 infection as the patient himself had bullous pemphigoid history and received systemic steroid treatments, the case report gave clear presentation of HHV-
6 corneal endothelitis diagnostic though which was meaningful for clinicians. Just one question, please add the baseline of endothelial cells condition and EDCs after anti-virus treatment.

Replay: (Main text, Line from 105 to 106) The baseline data of endothelial cells did not exist before the manifestation of the HHV-6A corneal endothelitis, unfortunately. As we have already mentioned in the paper, the endothelial cell density was 2719 cells/mm2 OD and 1733 cells/mm2 OS at the onset of corneal endothelitis. This time, we added the information of endothelial cell densities of one-year follow-up examinations. The endothelial cell density was 2786 cells/mm2 OD and 2545 cells/mm2 OS, respectively at the one-year follow-up examinations.

The reason why the cell density OS increased after anti-virus treatment may be that we could not measure the cell density correctly at the onset of corneal endothelitis because of corneal inflammation. We attached the two photos of corneal endothelial cells before and after treatment as supplementary materials.

Adel Ebraheem (Reviewer 3): Dear Dr. Ishida,

I would like to thank you for submitting this interesting case. However, we have some questions about your case report

1) For how long the patient was on steroid treatment?

Replay: (Main text, Line from 70 to 73) We added the information of the length of medical histories. The steroid therapy started with prednisolone 20mg/ day 2 years ago, gradually tapered, and had continued with 5mg/day for the last 6 month.

2) Could you share with us more about his/her medical history such as if he/she was diabetic?

Replay: (Main text, Line from 70 to 71) We added the information of the length and treatment of diabetes. He was diagnosed as diabetes 7 years ago and had been taking an oral anti-diabetic drug, miglitol 50mg 3 times daily.

3) As you know, steroid might increase the risk of herpes infection; we would like to know if the patient was on steroid when he/she got herpes infection. If he/she stopped the steroid, when did he stopped taking steroid?

Replay: (Main text, Line 71 to 73) The patient was on steroid when he got herpes infection, and he continued to use systemic steroid with 5mg/day during this episode. We added the information of the length and details of the steroid treatment.

(Main text, Line 98) Also we changed the sentence to inform that the patient did not stop taking steroid.
4) in the abstract, (line 38) there is a mistake about the reported visual acuity.

Replay: (Abstract, Line 38) We corrected the VA value to 2/200

We hope this manuscript is acceptable for publication in the BMC Ophthalmology.

Sincerely yours,

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