Title: Intraoperative and fluorescein angiographic findings of a secondary macular hole associated with age-related macular degeneration treated by pars plana vitrectomy

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Author's response to reviews: see over
Editors

BMC Ophthalmology
Ms. Erica Cruz and Dr. Haoyu Chen
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September 16, 2014

Dear Ms. Erica Cruz and Dr. Haoyu Chen:

Please find attached our revised manuscript MS: 1402341621135254 titled, “Intraoperative and fluorescein angiographic findings of a secondary macular hole associated with age-related macular degeneration treated by pars plana vitrectomy,” which we are submitting for consideration as a “Case Report” in BMC Ophthalmology.

We have addressed all the comments raised by the reviewers.

According to the reviewer 1’s comments, we added to show the OCT images and indocyanine green angiograms (IAs) for all 3 time points including before the AMD treatment, after macular hole development, and after vitrectomy and macular hole closure, revising both Figures 1 and 2. Because CNV lesion judged by the IA was not clearly enlarged, and the enlarged area observed in the FA seemed to be, at least in part, due to the enlargement of the area of RPE atrophy, we revised the conclusion; we weakened the hypothesis that the CNV has contracted and contributed to the pathogenesis, and added the pathological change in the RPE that may cause the vulnerability of the retinal tissue.

We look forward to hearing from you soon.

Thank you.

Sincerely,

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Point-by-point responses to the reviewers’ comments

Reviewer: Dr. Wataru Saito
Reviewer's report:
Minor essential revision
The authors described intraoperative findings (the presence of sticky ERM and ILM adhered to the retina strongly) in a patient with the development of macular hole (MH) after intravitreal injections of anti-VEGF therapy for wet type age-related macular degeneration (AMD). They speculated that these findings were due to an inflammatory reaction following the onset of AMD and/or anti-VEGF antibody injection-related reaction. Since these intraoperative findings of the vitreoretinal interface in eyes with secondary MH following the onset of AMD were rarely reported, this is an article whose findings are important to those with closely related research interests.

1. In Figure 1, images of indocyanine green angiography and optical coherence tomography at the initial visit should be added, because of verifying the presence of CNV in this case.

We thank the reviewer for understanding the value of this report and good advice. We added an indocyanine green angiogram (IA) and an optical coherence tomography (OCT) image at the initial visit in the revised Figure 1C, and 1D, respectively. A very thin CNV was observable in the OCT image that corresponded to the CNV indicated in the IA image. We revised the manuscript and the legend as follows;

Page 5, line 22~
In August 2009, a 78-year-old man presented with impaired central vision in his right eye and was diagnosed with wet AMD accompanied by subretinal fluid (Fig. 1A-D). …

Page 10, line 4~
(B) A FA obtained prior to the initial intravitreal injection revealed leakage from the CNV of occult with no classic-type (arrows). (C) An IA obtained prior to the initial intravitreal injection supported this finding showing the CNV (arrowheads). (D) An OCT image prior to the initial intravitreal injection showed subretinal fluid.
2. In Figure 2B, and 2G, the authors appear to describe that macular hyperfluorescence in fluorescein angiography (FA) is the area of CNV. In patients with occult CNV, however, I consider that to evaluate the area of CNV using only FA is difficult and the images of indocyanine green angiography and OCT corresponding to the region with the presence of CNV at the onset of MH are needed to verify enlargement of the CNV tissue.

Thank you for your comment. I agree with you that FA image is not enough to evaluate the occult CNV area. According to your advice, we added IA images at these time points which indicate the CNV area. The OCT images at these time points were already shown in the original figure (and the revised Figure 2D and 2F, respectively). The images included in the original figure were the horizontal scan, and we also have the vertical scan, but they were similar to the horizontal ones which were already shown.

We appreciate you again, and also apologize, that we corrected the evaluation of the CNV lesion; according to the IA image, the CNV lesion seemed not to be enlarged. We apologize for the misleading description in the original manuscript. The enlargement of the hyperfluorescent area observed in the FA may have included the increase the RPE’s atrophic change caused by the exudative change from the CNV. We revised the manuscript as follows;

Page 6, line 10~
A fluorescein angiogram (FA) and an indocyanine green angiogram (IA) showed that the CNV still existed, and the hyperfluorescent area in the FA expanded toward halfway around the fovea (Fig. 2B) which may have included atrophic change in the RPE.

Page 6, line 23~
The CNV tissue together with the RPE change secondarily caused by the CNV lesion surrounding the fovea remained post-operatively, as demonstrated by a FA and an IA (Fig. 2H, I).

Page 10, line 12~ (legend)
(B) A FA obtained after the diagnosis of the macular hole showed enlargement of the hyperfluorescent area (arrows). (C) An IA obtained after the diagnosis of the macular hole showed the CNV (arrowheads).

Page 10, line 20~ (legend)
(H) Hyperfluorescent area in a FA was clearly observed post-operatively (arrows) after the vitrectomy and the cataract extraction. (I) An IA showed that the CNV remained after macular hole surgery and its closure (arrows).
Moreover, we revised the discussion part including the RPE change as the underlying pathological changes related to macular hole development in the AMD eye, and weakened the hypothesis that the CNV has contracted and contributed to the pathogenesis. We revised the conclusion as follows:

**Page 3, line 19~ (abstract)**

Changes in the condition of his AMD and the RPE were observed on a fluorescein angiogram (FA) and an indocyanine green angiogram (IA) that preceded macular hole development, suggesting that subretinal changes may also have been involved in the pathogenesis.

**Page 7, line 16~**

Moreover, the subretinal condition due to AMD preceded macular hole development, suggesting that the pathological RPE may have induced retinal vulnerability, and the CNV might have contracted and accelerated the tangential traction from the subretinal side, and both of which may have possibly contributed to macular hole development.

**Page 8, line 4~**

However, in the case presented here, there are multiple possibilities for the underlying mechanism of the macular hole development, such as the pathological changes in the subretinal condition including CNV and the RPE, the chronic progression of vitreous modifications due to exudative changes caused by AMD, and intravitreal injections, which cause a sticky ERM and ILM changes.

**Page 8, line 12~**

These clinical data, including the intraoperative findings and the temporal changes related to AMD, suggest that an inflammatory reaction at the vitreo-retinal interface and subretinal pathological changes contribute to retinal conditions in AMD cases that are treated with intravitreal injections.
Reviewer: Dr. Dominik Odrobina

Reviewer's report:

Major Compulsory Revisions:

This case is interesting, however, a few things should be corrected. The author should add OCT picture prior to pegaptanib injection. At angiography picture after the vitrectomy cannot be concluded that the area indicated by the arrows, is a neovascular membrane. It seems to me that this area may be damage to the retinal pigment epithelium which is visible in the OCT picture. So you cannot say that the neovascular membrane is one of the factors causing the formation of a macular hole.

We appreciate the reviewer for the interest in this case, and the constructive advice. We added an OCT image obtained prior to the pegaptanib treatment in the revised Figure 1D. Since reviewer 1 recommended to add indocyanine angiogram (IA) to show the CNV, we also added an IA image in the revised Figure 1C.

Page 5, line 22–
In August 2009, a 78-year-old man presented with impaired central vision in his right eye and was diagnosed with wet AMD accompanied by subretinal fluid (Fig. 1A-D)….

Page 10, line 5–
(C) An IA obtained prior to the initial intravitreal injection supported this finding showing the CNV (arrowheads). (D) An OCT image prior to the initial intravitreal injection showed subretinal fluid.

We agree that the pointed part in the FA after vitrectomy was not the exact area of the CNV, seeing an IA image in the revised Figure 2I. We also agree that the change in the CNV area was not clear; the hyperfluorescent area observed in the FA would include the enlarged area of the pathologically changed RPE. We revised the manuscript as follows;

Page 6, line 23–
The CNV tissue together with the RPE change secondarily caused by the CNV lesion surrounding the fovea remained post-operatively, as demonstrated by a FA and an IA (Fig. 2H, I).
(H) Hyperfluorescent area in a FA was clearly observed post-operatively (arrows) after the vitrectomy and the cataract extraction. (I) An IA showed that the CNV remained after macular hole surgery and its closure (arrows).

Consistent with these changes, we revised the discussion part including the RPE change as the underlying pathological changes related to macular hole development in the AMD eye, and weakened the hypothesis that the CNV has contracted and contributed to the pathogenesis.

Changes in the condition of his AMD and the RPE were observed on a fluorescein angiogram (FA) and an indocyanine green angiogram (IA) that preceded macular hole development, suggesting that subretinal changes may also have been involved in the pathogenesis.

Moreover, the subretinal condition due to AMD preceded macular hole development, suggesting that the pathological RPE may have induced retinal vulnerability, and the CNV might have contracted and accelerated the tangential traction from the subretinal side, and both of which may have possibly contributed to macular hole development.

However, in the case presented here, there are multiple possibilities for the underlying mechanism of the macular hole development, such as the pathological changes in the subretinal condition including CNV and the RPE, the chronic progression of vitreous modifications due to exudative changes caused by AMD, and intravitreal injections, which cause a sticky ERM and ILM changes.

These clinical data, including the intraoperative findings and the temporal changes related to AMD, suggest that an inflammatory reaction at the vitreo-retinal interface and subretinal pathological changes contribute to retinal conditions in AMD cases that are treated with intravitreal injections.