Author’s response to reviews

Title: Improvements in visual acuity and macular morphology following cessation of antiestrogen drugs in a patient with anti-estrogen maculopathy resembling macular telangiectasia type 2: a pathogenic hypothesis

Authors:

Akihiro Shinkai (shinkai@huhp.hokudai.ac.jp)
Wataru Saito (wsaito@med.hokudai.ac.jp)
Yuki Hashimoto (mamepopposeat@yahoo.co.jp)
Susumu Ishida (ishidasu@med.hokudai.ac.jp)

Version: 2 Date: 08 Nov 2019

Author’s response to reviews:

November 7, 2019

Dr. Lingling Tian, Editor
BMC Ophthalmology

Re: Manuscript No. BOPH-D-19-00360R2
Improvements in visual acuity and macular morphology following cessation of anti-estrogen drugs in a macular telangiectasia type 2-like case: a pathogenic hypothesis

Dear Dr. Tian,

We appreciate your careful and favorable review of our manuscript and the guidance provided for a revision. As requested, we have revised the manuscript, which contains several corrections according to the guidance provided for the revision. The newly added sentences and phases are shown in the revision. Please find below our point-by-point responses to each of reviewers’ comments.

Editor Comments:
In ‘Consent for publicaiton', it is stated that 'Written informed consent was obtained from the patient’s parent for publication of this Case report and any accompanying images'. Please clarify why the consent was obtained from the parent? In this case, the patient was a 53-year-old woman.

We apologize for our mistake. We have made the following revision.

Page 13, lines 8-9
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.
Reviewer #2:
The reviewers have addressed the majority of my concerns. It is an interesting case that highlights the potential reversibility of tamoxifen toxicity. This is likely due to the relatively low dose the patient had taken. I understand that the authors are hypothesizing that tamoxifen toxicity shares similar pathologic features of MacTel2 and that they potentially share common pathophysiology. While the phenotypes may be similar it is still unclear whether or not the underlying mechanisms are the same. Are the authors suggesting that the etiology of MacTel2 is due to the RPE? Please clarify the following points in the text, and clearly state in the text:

We appreciate the reviewer’s encouraging comments as well as constructive critiques that we believe have made the revision more compelling. Please see below.

1. If the authors believe that tamoxifen toxicity is due to damage to the RPE. Do they also believe that MacTel2 is due to RPE dysfunction as well? This contrasts with the belief that MacTel2 is Muller cell mediated. Please explain this conflicting points of view in the text.

We appreciate the reviewer’s comments to improve our manuscript. Interestingly, an article published recently have demonstrated that abnormality of serine metabolism plays a role in the pathogenesis of photoreceptor impairment observed in patients with MacTel-2. Moreover, abnormality of the metabolism may cause the RPE impairment as well, because the article stated demonstrated that deoxysphingolipids with cytotoxicity, which were produced by abnormal serine metabolism, were elevated in not only the photoreceptor but RPE cells. Based on these observations, we have added fruitful discussion with new references as follows, regarding the pathogenesis of the development of findings resembling MacTel-2 observed in patients taking tamoxifen.

Page 3, lines 3-1 from the bottom
From these results and the previous observations, toxicity of both photoreceptor and RPE cells caused by anti-estrogen drugs may contribute to the development of anti-estrogen maculopathy similar to MacTel-2.

Page 8, lines 11-Page 9, lines 9
Moreover, multimodal imaging in patients with MacTel-2 of very early stage revealed a decrease of cone density even when macular EZ was intact [10]. These observations suggest photoreceptor damage prior to Müller cell impairment. Interestingly, a study published very recently have demonstrated elevated levels of cytotoxic deoxysphingolipids following a decrease in serum serine levels in MacTel-2 patients with idiopathic etiology as well as gene mutation of serine metabolism [11]. Deoxysphingolipids induced photoreceptor apoptosis in human retinal organoids and mice supplemented with serine diet showed decreased photopic response on electroretinography [11]. These results indicate that abnormality of sphingolipid metabolism plays a role in the pathogenesis of the photoreceptor loss observed in patients with MacTel-2. Importantly, it has been reported that tamoxifen suppresses sphingolipid metabolism [12]. Therefore, chronic retinal damage following tamoxifen-induced impairment of sphingolipid metabolism may be involved in the pathogenesis of MacTel-2-like findings associated with patients taking tamoxifen.
In mice with serine diet, elevated deoxysphingolipids were observed in the RPE as well. The elevation of the cytotoxic metabolites is theorized to affect the RPE [11].

Page 9, lines 6-4 from the bottom
Moreover, tamoxifen and toremifene cause RPE cell death by inhibiting phagocytosis of the rod’s outer segments by RPE cells due to lysosomal destabilization [14, 15].
Thus, tamoxifen-induced adverse effects on sphingolipid metabolism and lysosomal function in RPE cells may be involved in the development of MacTel-2-like findings in patients taking tamoxifen.

New references

2. Do the authors believe that tamoxifen is directly effecting Muller cells?

Thank you. According to the reviewer’s suggestion, we have added the following sentences.

Little is known about tamoxifen’s effect on Müller cells. Tamoxifen-induced abnormality of sphingolipid metabolism may possibly affect Müller cells as well as photoreceptor cells.

We appreciate the reviewers’ thoughtful and constructive critiques. We believe that the revision addresses all the points raised by the reviewers. These valuable comments have further improved the overall quality of our manuscript. For all reasons, we believe that the revised manuscript will now be acceptable for publication in BMC Ophthalmology.

Sincerely,

Wataru Saito, M.D., Ph.D.
Visiting Clinical Professor at Department of Ophthalmology,
Faculty of Medicine and Graduate School of Medicine, Hokkaido University