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

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Author’s response to reviews:

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Dr. Guangde Tu, Editor
BMC Ophthalmology
Re: Manuscript No. BOPH-D-19-00360R1
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. Tu,

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 red in the revision. Please find below our point-by-point responses to each of reviewers’ comments.

Reviewer #1:
1. I commend the authors for a well-written manuscript.

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

2. This is a typical case of tamoxifen maculopathy. The fluorescein angiography is not consistent with the diagnosis of macular telangiectasia. There are very few reports in the literature on toremifene maculopathy or on the effect of stopping anti-estrogen drugs on the retinal morphology of patients with anti-estrogen maculopathy. Hence the value of this report. I suggest changing the title (and the text) to reflect both facts without reference to macular telangiectasia.
We appreciate the reviewer’s comments to improve our manuscript. We agree that the present case can be diagnosed with tamoxifen retinopathy (anti-estrogen maculopathy), in addition to rarities of previous reports on medical history of toremifene use and improvement of macular morphology following cessation of anti-estrogen drugs. The reviewer may think that tamoxifen retinopathy and MacTel-2 are apparently distinct clinical entities from a standpoint of difference in the possible pathogenesis (RPE toxicity v.s. Müller cell dysfunction). However, we consider that the mechanism causing impairment of the Müller cells in MacTel-2 has not been determined yet. Patients with MacTel-2 at the initial stage have abnormalities of the ellipsoid zone and/or fundus autofluorescence prior to the presence of foveal inner and outer lamellar cavities on optical coherence tomography, suggesting impairment of the photoreceptors and RPE cells preceding loss of Müller cells. In the MacTel study (reference 5), moreover, it has been already described that clinical findings of tamoxifen retinopathy are similar to those of MacTel-2. Based on the present case’s findings, previous observations regarding mechanism causing tamoxifen retinopathy (toxicity for RPE cells), and similarity of clinical findings between tamoxifen retinopathy and MacTel-2, we would like to focus on the pathogenesis causing clinical findings resembling MacTel-2 in patients with tamoxifen retinopathy in this manuscript. This observation would serve for further understanding of considering the pathogenesis of MacTel-2. Therefore, we have made the following revision for our manuscript with new references, without deleting description of MacTel-2 throughout manuscript.

Page 1, lines 1-3
Improvements in visual acuity and macular morphology following cessation of anti-estrogen drugs in a patient with anti-estrogen maculopathy resembling macular telangiectasia type 2: a pathogenic hypothesis

Page 3, lines 4-6
Here we report a case with anti-estrogen maculopathy resembling MacTel-2 with improved visual function and macular morphology following cessation of anti-estrogen drugs.

Page 3, lines 2 from the bottom-Page 4, line 1
From these results and the previous observations, toxicity for the RPE caused by anti-estrogen drugs may contribute to the development of anti-estrogen maculopathy similar to MacTel-2.

Page 5, lines 4-13
Anti-estrogen drug-associated retinopathy has been reported to result basically from use of tamoxifen, as called tamoxifen retinopathy; however, there were few reports on toremifene use [3]. Treatment strategy for tamoxifen retinopathy is cessation of the drug. Visual function may stabilize after treatment but commonly be unrecoverable [4]. Findings such as intraretinal crystals, RPE abnormality, and foveal hypo-reflective space on optical coherence tomography (OCT), as seen in patients with tamoxifen retinopathy, may also be observed in patients with macular telangiectasia type 2 (MacTel-2), showing similarity of clinical findings between the two diseases [5].

Page 5, lines 3-1 from the bottom
We herein report a case with anti-estrogen maculopathy resembling MacTel-2 showing improved visual acuity and macular morphology following cessation of anti-estrogen drugs.

Page 6, lines 6-3 from the bottom
Enhanced depth imaging OCT (EDI-OCT) revealed loss of the ellipsoid zone (EZ) and interdigitation
zone (IZ) OU, inner lamellar cavity OS, and outer lamellar cavity OU at the macula, all of which were part of typical MacTel-2 findings (Fig. 2A, B).

Page 7, line 2 from the bottom-Page 8, lines 3
We encountered an anti-estrogen maculopathy case exhibiting part of typical MacTel-2 findings. In this case, use of toremifene and marked improvements of the BCVA and macular morphology following cessation of anti-estrogen drugs were rarely described in the literature.

Page 8, lines 10-12
Collectively, our findings and those of previous studies suggest that toxicity for the RPE, caused by anti-estrogen drugs, is involved in the development of anti-estrogen maculopathy.

Page 8, lines 6 from the bottom-Page 9, line 13
Clinical findings in the present case resembled those of MacTel-2 at the early stage except for the absence of dye leakage at the temporal side of the macula on fluorescein angiography. In patients with MacTel-2, Müller cell dysfunction has been proposed following histopathological examination [11], as being observed as inner and outer lamellar cavities at the fovea on OCT. However, the mechanism causing the Müller cell abnormality remains unresolved. Patients with MacTel-2 at the initial stage have disruptions of the EZ despite the lack of foveal inner and outer lamellar cavities [12], suggesting photoreceptor damage prior to Müller cell impairment. On FAF, RPE impairment occurs prior to OCT and angiographic changes in MacTel-2 [13], suggesting impairment of the RPE preceding abnormalities of Müller cells and photoreceptors. In our case, RPE impairment actually improved following the cessation of the drugs but persisted despite marked improvements of inner and outer lamellar cavities and the EZ on OCT. A recent study with a model of photoreceptor degeneration revealed that loss of rod cells was simultaneously associated with damage to the neurovascular unit comprising photoreceptors, RPE, and Müller glia [14], suggesting a coexisting interaction between the photoreceptor/RPE cells and Müller glia. Therefore, impairment of the photoreceptors and Müller cells paralleling the RPE toxicity caused by anti-estrogen drugs may play a role in the development of MacTel-2-like findings in the present case.

Page 10, lines 5-1 from the bottom
In conclusion, BCVA, macular morphology, and impairment of the RPE improved following cessation of anti-estrogen drugs in an anti-estrogen maculopathy case with MacTel-2-like findings. These results suggest the relationship between retinal toxicity of anti-estrogen drugs and the development of findings resembling MacTel-2 in the present case.

New references


Reviewer #2:
1. Authors have reported a case which is crucial to be published for supporting to fellow medical doctors. They described and interpreted well the case which can be easily followed. Background of the paper is well written, outlining the necessity of reporting such cases. The authors present an interesting case of tamoxifen / toremifine toxicity with MacTel2-like features.

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

2. The case is consistent with previous reports of early tamoxifen toxicity. I would not call this toxicity MacTel2-like as the primary defect in MacTel2 is thought to be the muller cells, it may be confusing to compare the two retinopathies, unless the authors also believe the muller cells are involved.

Thank you for the reviewer’s comments to improve our manuscript. This is a valid point to determine the value of this paper. We agree that the present case can be diagnosed with tamoxifen retinopathy (anti-estrogen maculopathy), and that Müller cells are indeed impaired in MacTel-2. Please see above on Reviewer 1, Point 2.

3. The unusual aspect of this is the recovery of the ellipsoid layer / photoreceptors in this patient. It should be noted that there still appears to be persistent disruption of the interdigitation zone or the interface between the recovering photoreceptors and the RPE. This suggests to me that there may still be persistent RPE loss. The RPE cells may potentially migrate or grow larger to compensate for their loss. It has been previously believed that the toxicity is irreversible, however the authors present some evidence of reversibility of photoreceptor loss as determined by OCT.

Thank you for the reviewer’s constructive comments. This is a valid point. In our revised manuscript, we have emphasized the unusual aspect of recovery of the photoreceptors in this case with anti-estrogen maculopathy. Please see above on Reviewer 1, Point 2. Moreover, we agree with the presence of persistent interdigitation zone loss and RPE dysfunction in the present case. Therefore, we have added the following sentences and phrases.

Page 6, lines 6-5 from the bottom
Enhanced depth imaging OCT (EDI-OCT) revealed loss of the ellipsoid zone (EZ) and interdigitation zone (IZ) OU.

Page 7, lines 10-11
However, the loss of the foveal IZ persisted.

Page 7, lines 5-4 from the bottom
The macular morphology remained unchanged OU. The hyper-autofluorescence area on FAF was smaller but persisted (Fig. 1H).

Page 8, lines 5-7
In the present case, hyper-autofluorescence on FAF and the loss of foveal IZ on OCT persisted despite restored macular EZ following cessation of anti-estrogen drugs, suggesting persistent RPE dysfunction.

Page 9, lines 4-7
In our case, RPE impairment actually improved following the cessation of the drugs but persisted despite marked improvements of inner and outer lamellar cavities and the EZ on OCT.

Page 17, lines 2 from the bottom-Page 18, line 1
(A, B) At the initial visit, the loss of ellipsoid zone (EZ), interdigitation zone, and outer lamellar cavity at the fovea were observed in both eyes.

Page 18, lines 7
However, the loss of the interdigitation zone at the fovea persisted.

4. As the authors are presenting hypotheses for the mechanism of action, they should consider that drugs such as tamoxifen can in itself induce cell death to the RPE (through myriad cell death mechanisms) via disruption of the lysosome and lysosomal activity. Anti-estrogen drugs in themselves may induce apoptosis, as estrogen is itself a potent anti-apoptotic agent. It is interesting but not surprising to see the photoreceptors appear to recover suggesting some resistance of the photoreceptors to tamoxifen toxicity, further suggesting the RPE is the primary target of tamoxifen.

I appreciate the reviewer’s constructive comments for our hypotheses. According to the reviewer’s comments, we have made several revisions. Please see Pages 8, lines 4-12 in our revised manuscript.

5. It is difficult to assess which aspect of the toxicity is reversible, is it the tamoxifen toxicity or the toremifine toxicity? The difference between the two drugs should be considered, though I believe they are structurally very similar.

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

Page 10, lines 2-6
Toremifene is structurally and pharmacologically similar to tamoxifen. A previous study showed that there was no significant difference in frequency of retinopathy between patients receiving tamoxifen or toremifene three years after the start of the drugs [3]. Therefore, it is difficult to determine whether which drug caused retinal toxicity in the present case.

6. This is overall an interesting case and provides some evidence of reversibility of anti-estrogen retinopathy. In addition to the duration of treatment, could the authors also include the total dosage of tamoxifen and toremifene, as I would assume it is a relatively smaller dose.

Thank you for your comments. According to the reviewer’s comments, we have added the following sentences and phrases.

Page 6, lines 3-6
The patient received oral tamoxifen 20 mg/day for 58 months (cumulative dose; 34.8 g) and thereafter toremifene 40 mg/day for 11 months (cumulative dose; 13.2 g) for breast cancer; however, toremifene was discontinued several days prior to her first hospital visit.

Page 10, lines 6-9
Tamoxifen retinopathy usually appears to occur when patients received total cumulative dose of greater than 100 g [1]. The total cumulative dose administered in this case was much less than 100 g. This may be one reason why photoreceptors recovered in this case.
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,

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