Reviewer’s report

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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Reviewer: Leo Am Kim

Reviewer's report:

The authors present an interesting case of tamoxifen / toremifine toxicity with MacTel2-like features. 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. 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. 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 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. 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. 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 toremifine, as I would assume it is a relatively smaller dose.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Are the conclusions drawn adequately supported by the data shown?
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