Author's response to reviews

Title: Peripheral capillary nonperfusion in asymptomatic Waldenstrom's macroglobulinemia

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Author's response to reviews:

Re: “MS: 1535410802394906
Peripheral capillary nonperfusion in asymptomatic Waldenstrom's macroglobulinemia”

Dear Editor,

Thank you for your interest in our manuscript and your comments which really add to its clarity.

Please find attached the revised submission of the manuscript entitled “Peripheral capillary nonperfusion in asymptomatic Waldenstrom's macroglobulinemia” according with all the instructions of the reviewers.

The detailed response to the comments follows:

Reviewer 1
Comment:
This is an interesting report.

Major compulsory revisions:
1. What was the result of recent laboratory testing apart from the one value given (e.g., serum viscosity level, total protein)?
2. Were other causes of peripheral hypoperfusion ruled out?

Minor essential revisions:
1. There are a few minor grammatical mistakes.

Response:
(1) The first sentence of the case presentation has been changed to “A 39-year-old male with a recent diagnosis of asymptomatic Waldenström's macroglobulinemia confirmed with bone marrow biopsy (IgM: 2.3 g/L, total
protein 10.4 gr/dl) was referred from his internist to our clinic for ocular evaluation.”

(2) All other systemic or ocular diseases that could possibly induce peripheral hypoperfusion were ruled out in our case.

(3) The manuscript has now been edited and we believe its free of grammatical/typographical errors.

Reviewer 2
Comment:
Authors can consider mentioning angiography findings in the Left eye as well along with mentioning the refractive status of eye under investigation (as the other eye was mentioned to be myopic). Changes are expected to be bilateral in the disease under consideration and presence of only unilateral changes may point to an alternate hypothesis which may include operated vitrectomy procedure as well.

Response:
(A) We completely agree with the reviewer that changes are expected to be bilateral in the disease, however the fellow eye of the patient had undergone vitrectomy and extensive peripheral cryotherapy for the treatment of retinal detachment as a result of which changes in the capillary perfusion could not be evaluated with angiography.

The sentence “…capillary non-perfusion would be expected to be bilateral, however, this could not be evaluated in the fellow eye of our patient, where extensive cryotherapy had been applied during vitrectomy for the treatment of the retinal detachment.” has been added in the discussion section.

(B) The refractive error of both eyes have been added in the manuscript.
Case presentation “Both eyes of the patient, were highly myopic (13D OU).”

Reviewer 3
Comment:
Koutsandrea et al present a case of peripheral retinal capillary non-perfusion associated with asymptomatic Waldenström's macroglobulinemia.
Here are my comments:
In the conclusion the authors state that main retinal findings of hyperviscosity syndrome (HVS) are central retinal hemorrhages and vein dilation. Based on our findings this is not true. Central changes are just more easily to observe since it requires only simple ophthalmoscopy. These changes represent the more/most severe findings, but not necessarily the main findings. Venous dilation seem to be the first signs of HVS followed by peripheral retinal hemorrhages, which can
only be observed by indirect ophthalmoscopy with scleral depression. Only in advanced HVS one can find central venous dilation, increased tortuosity, central hemorrhages, disc edema, and venous sausaging. In this particular case the authors state that WM was asymptomatic. It would be very interesting to know the serum viscosity levels in this patients (not stated). Right now, the reader does not know if the patient had in fact a HVS. Retinal blood flow analysis of retinal macrocirculation has shown that autoregulation of the retinal blood flow leads to dilation of the retinal veins to maintain normal retinal blood flow over a wide range of IGM and serum viscosity levels. Only at extreme IGM and serum viscosity levels the autoregulation fails and blood flow decreases. Therefore the clinical appearance of vein occlusion is most of the times misleading. Even in severe cases, the retinal bloodflow can remain normal although it looks like an occlusion. Capillary nonperfusion, as shown in this case, would be suspected only at very high serum viscosity levels or if capillary dilation is not sufficient due to some other underlying pathologic conditions. Therefore there is also the question if the high myopia in this patient makes the capillary meshwork more susceptible to damage/occlusion in HVS. From my own experience with this rare disease, capillary nonperfusion is in fact a very uncommon manifestation. Based on the presented images the areas of nonperfusion are rather small. Since color images of the peripheral fundus are not presented, we can not even verify that these are areas of capillary nonperfusion and not just peripheral hemorrhages blocking the background fluorescence. I strongly suggest to add color images of the peripheral retina in the area of assumed nonperfusion. Comment:

(A)Paragraph 2 of the conclusions has been changed to “Menke et al2 have recently reported that these changes represent the more/most severe findings, but not necessarily the main findings. Venous dilation seem to be the first signs of HVS followed by peripheral retinal hemorrhages, which can only be observed by indirect ophthalmoscopy. Only in advanced HVS one can find central venous dilation, increased tortuosity, central hemorrhages, disc edema, and venous sausaging,”

(B)The first sentence of the case presentation has been changed to “A 39-year-old male with a recent diagnosis of asymptomatic Waldenström's macroglobulinemia confirmed with bone marrow biopsy (IgM: 2.3 g/L, total protein 10.4 gr/dl) was referred from his internist to our clinic for ocular
evaluation.”

(C) The sentence “The fact that our patient was highly myopic should be also taken into consideration; it is not unlikely, that capillary meshwork is more susceptible to damage or to occlusion in patients with high myopia and hyperviscosity syndromes.” has been added in the discussion section.

(D) Unfortunately we don’t have color images of the peripheral retina.

Editorial office
Comment:
In addition to addressing the concerns of the reviewers, we ask that you modify your manuscript to conform to our journal standards
Response:
We have modified the text to conform with the journals standards.

Thank you for considering our manuscript for publication.

Sincerely yours,
Ilias Georgalas, MD
Consultant Ophthalmic Surgeon