American Journal of Ophthalmology Case Reports 26 (2022) 101498

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Peripheral retinal neovascularization in a patient with obstructive sleep apnea

Ravin Sajnani [a,b], Elena Karapetian [b], Abhinav Golla [a,b], Irena Tsui [a,b], David Sarraf [a,b,*]

[a] Stein Eye Institute, University of California - Los Angeles, 100 Stein Plaza Driveway, Los Angeles, CA, 90095, USA
[b] Greater Los Angeles VA Healthcare Center, West Los Angeles Veterans Affairs Hospital, Department of Ophthalmology, 11301 Wilshire Boulevard, Los Angeles, CA, 90073, USA

ARTICLE INFO

Keywords:
Diabetic retinopathy
Hypoxia
Ischemia
Nonperfusion
Obstructive sleep apnea
Peripheral retinal neovascularization

ABSTRACT

Purpose: To describe a case of peripheral retinal neovascularization and its possible etiological connection to comorbid obstructive sleep apnea.
Observations: In this case report we describe a diabetic patient with obstructive sleep apnea who presented with bilateral peripheral retinal neovascularization but in the absence of any other evidence of diabetic retinopathy. Aside from confirmed nocturnal hypoxia and reasonably controlled diabetes mellitus, etiological investigation was otherwise unrevealing.
Conclusions and Importance: In the absence of typical findings for diabetic retinopathy, nocturnal hypoxia due to obstructive sleep apnea may be a contributing factor in the development of peripheral retinal neovascularization. There may be a role for more vigilant OSA screening in patients with peripheral retinal neovascularization as treatment with positive airway pressure devices may reduce the retinal hypoxic burden.

1. Introduction

Obstructive sleep apnea (OSA) can lead to various significant systemic complications. Common ocular associations include floppy eyelid syndrome, non-arteritic anterior ischemic optic neuropathy, central serous chorioretinopathy, retinal vein occlusion, and glaucoma.[1] Nocturnal hypoxemia is implicated in the pathogenesis of these sequelae,[1] and although retinal hypoxia is a critical element in the development of retinal neovascularization (NV), NV secondary to OSA is not a clinically-described entity.

In this case report, we describe the isolated presence of peripheral retinal neovascularization in each eye of a well-controlled diabetic who failed to show any other evidence of diabetic retinopathy (DR). The patient did report OSA and prior sleep study was remarkable for significant nocturnal hypoxemia which may be a contributing factor in the development of proliferative retinopathy in this case.

2. Case report

A 51-year-old African American male presented to our clinic for comprehensive exam with nonspecific visual complaints. Past medical history was significant for type 2 diabetes mellitus treated with metformin twice daily, essential hypertension treated with lisinopril once daily, hyperlipidemia treated with atorvastatin once daily, obesity, and obstructive sleep apnea. The patient admitted non-compliance with usage of his continuous positive airway pressure (CPAP) apparatus. Family history was negative for sickle cell disease or trait or inherited retinal disease, and social history was negative for intravenous drug abuse. The remainder of the history was unremarkable, and other medications and allergies were non-contributory.

Best corrected visual acuity was 20/20 in each eye. Intraocular pressures and anterior segment exam were within normal limits in both eyes. Fundus photographs (Figs. 1 and 2) of the posterior pole were unremarkable, and the macula was flat and dry with no evidence of diabetic retinopathy (DR) or diabetic macular edema in either eye. However, isolated fronds of peripheral retinal neovascularization were noted temporally in both eyes and were associated with very small preretinal hemorrhages in each eye. There was a notable absence of signs of retinal vein occlusion or DR. Specifically there was no evidence of retinal venous tortuosity or beading and there were no signs of microaneurysms, dot and blot hemorrhages, hard exudates, or cotton wool spots.

Optical coherence tomography of the macula was entirely within normal limits in both eyes and there was no evidence of macular edema

* Corresponding author. Stein Eye Institute, 100 Stein Plaza Driveway, Los Angeles, CA, 90095, USA.
E-mail address: dsarraf@ucla.edu (D. Sarraf).

https://doi.org/10.1016/j.ajoc.2022.101498
Received 4 June 2021; Received in revised form 16 March 2022; Accepted 21 March 2022
Available online 3 April 2022

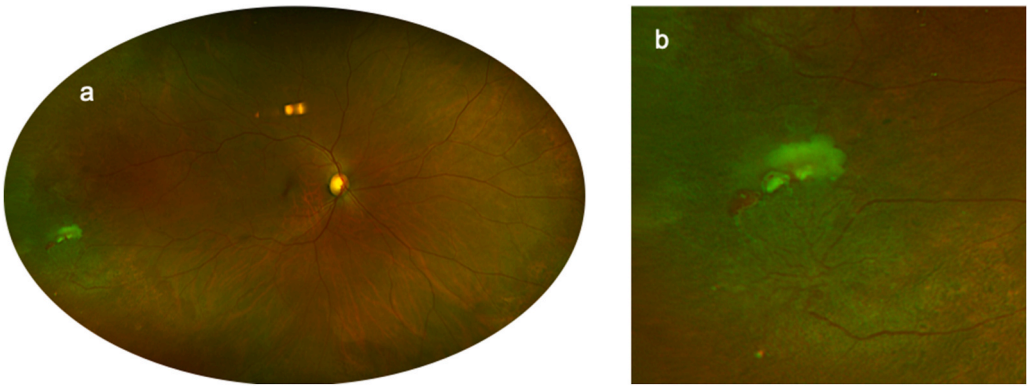

Fig. 1. Right eye. a) Widefield pseudocolor fundus photograph, and b) Magnified view illustrates peripheral retinal neovascularization.

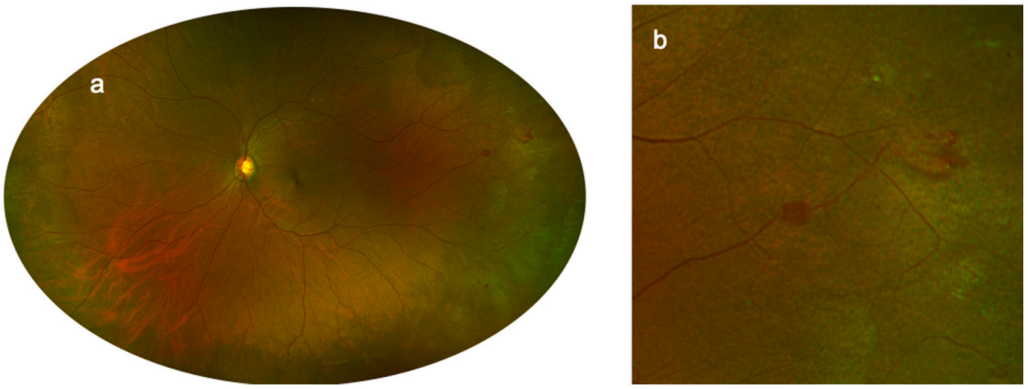

Fig. 2. Left eye. a) Widefield pseudocolor fundus photograph, and b) Magnified view illustrates peripheral retinal neovascularization.

or inner or middle retinal thinning[2] (Fig. 3). Widefield fluorescein angiography (Fig. 4) demonstrated temporal nonperfusion and leakage from the regions of retinal neovascularization, right eye greater than left eye. Of note, the fluorescein angiogram was entirely within normal limits in the posterior pole and midperiphery with no evidence of DR or microvasculopathy in either eye.

Systemic testing revealed a glycosylated hemoglobin (HbA1c) of 6.7% (average of 7.0% over the last 9 years) and notably a normal hemoglobin electrophoresis and unremarkable carotid doppler ultrasound. Further systemic testing for infectious and inflammatory vasculitis, hyperviscosity, and hypercoagulability mediators was negative (Table 1).

Recent sleep study revealed an apnea-hypopnea index of 19.1 and a nocturnal oxygen saturation <88% present for 4.6% of the patient's sleeping period. Regarding these results, apnea is defined as a pause in breathing of at least 10 seconds, hypopnea is a reduction in breathing flow for at least 10 seconds that is accompanied by a reduction in oxygen saturation or arousal from sleep, and the apnea-hypopnea index is a measure of how many apnea and hypopnea events occur per hour of sleep. Based on current classification schemata, an apnea-hypopnea index of 19.1 falls within the range of moderate OSA severity.[3]

Targeted retinal photocoagulation was performed to the temporal regions of nonperfusion in both eyes with the aim of induced regression of the neovascularization. The patient was additionally recommended to continue vigilant control of his diabetes, and CPAP compliance was strongly encouraged.

3. Discussion and conclusions

Peripheral retinal neovascularization occurs secondary to retinal hypoxia which can be due to a number of described etiologies.[4] In a review of 100 patients with peripheral retinal neovascularization, nearly half of the patients were found to have a sickling hemoglobinopathy, while 20% showed evidence of branch retinal vein occlusion and 9% displayed diabetic retinopathy. An etiologic factor could not be identified in 10% of the patients[5] who likely harbored milder, multifactorial causes of retinal hypoxia. As our patient lacked an otherwise clear etiology for retinal hypoxia, the possibility of hypoxia due to comorbid OSA with or without concomitant subclinical diabetic microvascular ischemia was entertained, which was supported by his diabetic (although well-controlled) HbA1c range and nocturnal hypoxia recorded during his sleep study.

While it is possible that OSA-induced nocturnal hypoxemia can cause sufficient retinal hypoxia to independently cause neovascularization, the more likely pathway is potentiation of other comorbid ischemic etiologies.[6] The combination of diabetic microvascular compromise and OSA-induced nocturnal hypoxemia may predispose to a higher incidence of diabetic retinopathy, and accordingly, a recent meta-analysis showed significantly increased risk of diabetic retinopathy with comorbid OSA.[7] Additionally, increased endothelial damage and vascular

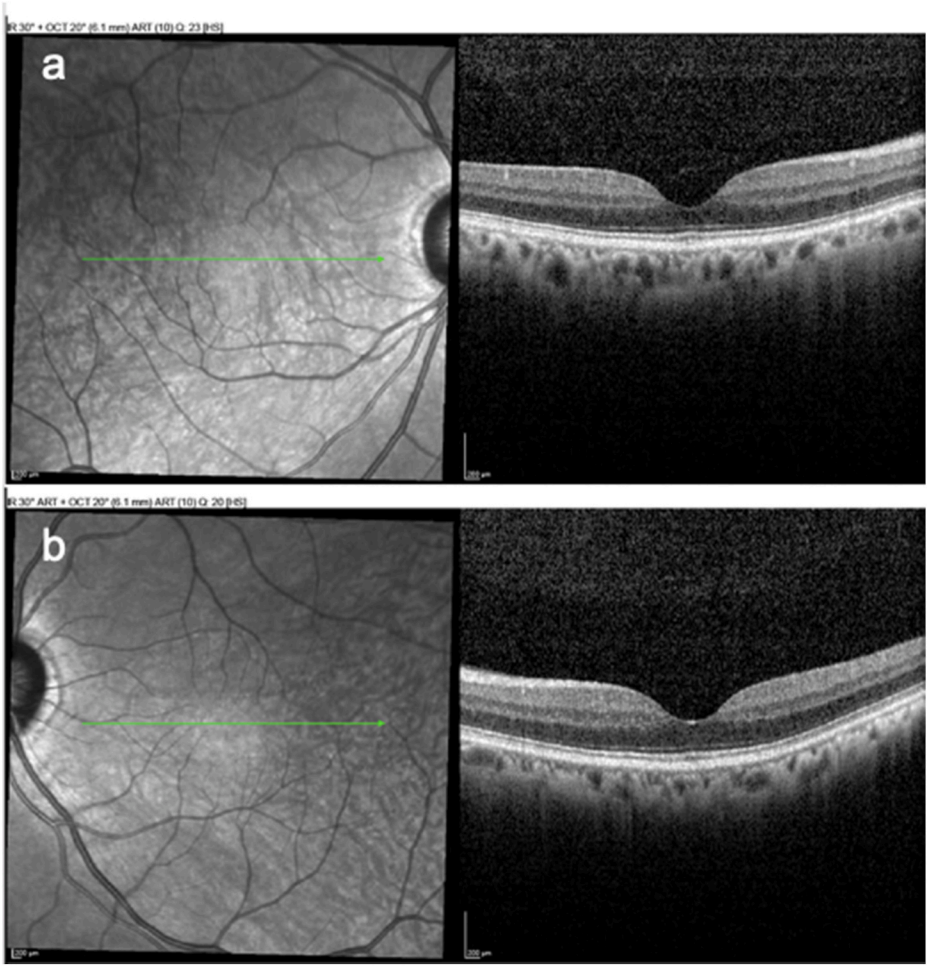

Fig. 3. Normal near-infrared images of the posterior pole and normal optical coherence tomography B-scans through the fovea for the a) right and b) left eyes.

stasis associated with OSA may heighten the risk for retinal venous occlusion.[6]

Since our patient lacked the classic stigmata of DR, venous occlusive disease, or other ischemic retinopathy and his comprehensive systemic workup was unremarkable aside from OSA, we believe OSA may have played a significant role in the development of peripheral retinal NV. However, one cannot discount the key role of diabetes as an important factor causing the development of retinal NV despite the excellent glycemic control and the absence of retinopathy in the posterior pole and periphery. Approximately 30–40% of cases of DR can be associated with predominantly peripheral findings.[8] In addition, Sarraf et al.[9] showed that African American diabetics with proliferative retinal disease can present with fewer, more occult, signs of DR unlike other demographics with advanced DR (e.g. Hispanic diabetics) who tend to display a more fulminant pattern of exudative retinopathy. Despite excellent diabetic control and the absence of the classic stigmata of DR, years of mild hyperglycemia may have caused pre-clinical diabetic microvascular damage. As such, in this case, nocturnal hypoxemia together with underlying diabetes, despite excellent control, may have conspired to cause peripheral retinal ischemia and neovascularization.

Treatment of OSA classically involves continuous positive airway pressure (CPAP) to prevent nocturnal airway collapse, and improved oxygenation may help improve or prevent worsening of retinal hypoxia. In a study of veteran patients with OSA, the prevalence of diabetic retinopathy was lower in those patients who were compliant with CPAP therapy even after controlling for HbA1c and time since diagnosis of diabetes mellitus.[10] Additionally, a recent study found that patients who underwent treatment of OSA were found to have normalization of OCT abnormalities, presumably due to correction of their nocturnal hypoxemia.[11] Patients with peripheral nonperfusion and neovascularization should receive targeted retinal photocoagulation and/or vascular endothelial growth factor antagonist intravitreal therapy which is the mainstay of treatment of proliferative retinopathy. Heightened awareness of the potential role of OSA to cause retinal hypoxia may suggest a greater need for OSA screening in patients, especially diabetics, with peripheral retinal neovascularization, as treatment with CPAP may reduce retinal hypoxic burden.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

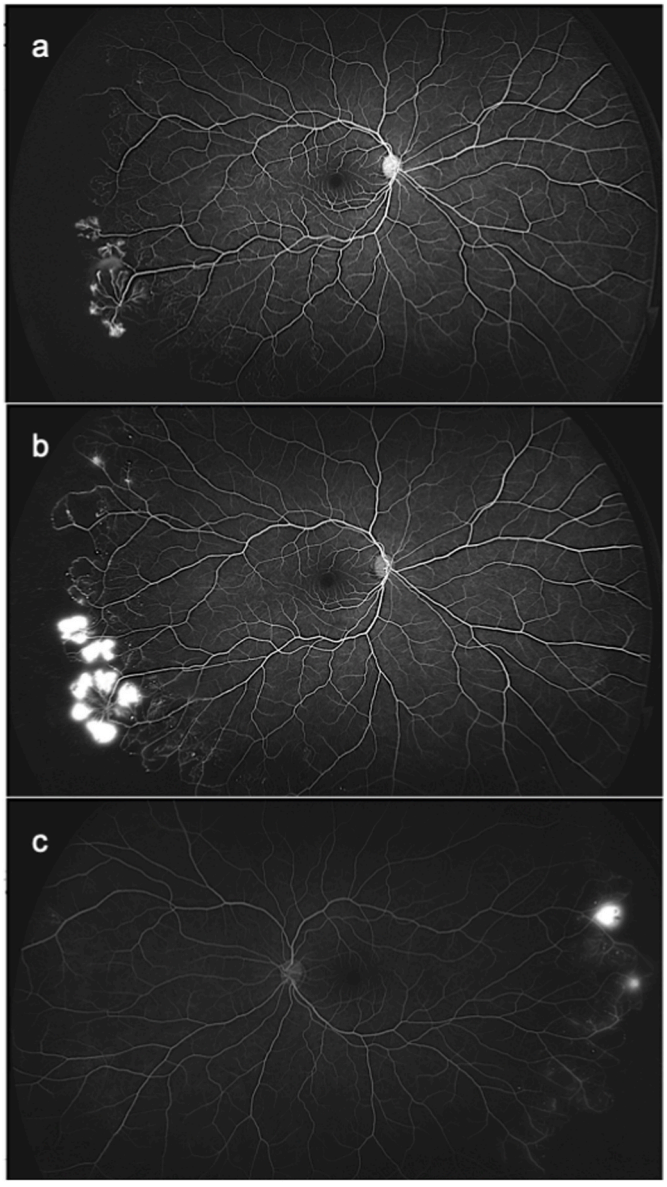

Fig. 4. Fluorescein angiography. a) Right eye venous phase and b) Right eye late venous phase show leakage at the site of peripheral retinal neovascularization, and c) Left eye late venous phase also shows leakage at the site of peripheral retinal neovascularization.

Table 1
Results of systemic testing.

Vitals	
Systolic blood pressure (mmHg, years 2014–2020)	101–131
Diastolic blood pressure (mmHg, years 2014–2020)	67–80
Atherosclerotic	
Lipid Panel	WNL
Carotid doppler ultrasound	No hemodynamically significant stenosis
HbA1c	Most recent = 6.7% Average over last 9 years = 7.0%
Infectious/Inflammatory	
RPR	Negative
Quantiferon-Gold	Indeterminate
TB1 and TB2	WNL
Inflammatory	
ACE	WNL
Chest X-ray	No bilateral hilar lymphadenopathy
ANA	Negative
ANCA	WNL
Hypercoagulability	
Anticardiolipin antibodies	WNL
Protein C and S activity	WNL
Hyperviscosity	
Serum electrophoresis	WNL
Urine electrophoresis	WNL
White blood cell count and hemoglobin	WNL
Other	
Hemoglobin electrophoresis	WNL (Hb-A 97%, Hb-A2 3%, Hb-F 0%)
Apnea-Hypopnea Index	19.1
Percentage of sleep with oxygen saturation <88%	4.6%

mmHg – millimeters of mercury, HbA1c – glycosylated hemoglobin, RPR – rapid plasma regain, TB1 and TB2 – tuberculosis-specific antigens, ACE – angiotensin converting enzyme, ANA – antinuclear antibody, ANCA – anti-neutrophil cytoplasmic antibody, WNL – within normal limits, Hb-A – hemoglobin A, Hb-A2 – hemoglobin A2, Hb-F – hemoglobin F.

Acknowledgements

We would like to extend our gratitude to the nurses and ophthalmic technicians in our clinic who are critical to the care we provide our patients daily.

References

1. Santos M, Hofmann RJ. Ocular manifestations of obstructive sleep apnea. *J Clin Sleep Med.* 2017;13(11):1345–1348. https://doi.org/10.5664/jcsm.6812.
2. Preti RC, Iovino C, Abalem MF, et al. Prevalence of focal inner, middle, and combined retinal thinning in diabetic patients and its relationship with systemic and ocular parameters. *Transl. Vis. Sci. Technol.* 2021;10(2):26. https://doi.org/10.1167/tvst.10.2.26.
3. Patel SR. Obstructive sleep apnea. *Ann Intern Med.* 2019;171(11):ITC81–ITC96. https://doi.org/10.7326/AITC201912030.
4. Jampol LM, Goldbaum MH. Peripheral proliferative retinopathies. *Surv Ophthalmol.* 1980;25(1):1–14. https://doi.org/10.1016/0039-6257(80)90071-5.
5. Brown GC, Brown RH, Brown MM. Peripheral proliferative retinopathies. *Int Ophthalmol.* 1987;11(1):41–50. https://doi.org/10.1007/BF02027896.
6. D'Souza H, Kapoor KG. Retinal vascular manifestations of obstructive sleep apnea. *Curr Opin Ophthalmol.* 2020;31(6):508–513. https://doi.org/10.1097/ICU.0000000000000698.
7. Zhu Z, Zhang F, Liu Y, et al. Relationship of obstructive sleep apnoea with diabetic retinopathy: a meta-analysis. *BioMed Res Int.* 2017;2017:4737064. https://doi.org/10.1155/2017/4737064.
8. Silva PS, Dela Cruz AJ, Ledesma MG, et al. Diabetic retinopathy severity and peripheral lesions are associated with nonperfusion on ultrawide field angiography. *Ophthalmology.* 2015;122(12):2465–2472. https://doi.org/10.1016/j.ophtha.2015.07.034.

Funding

No funding or grant support

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: RS, EK, AG, IT, DS.

9. Chen JL, Luviano DM, Chen JC, Yu F, Sarraf D. Comparison of diabetic retinopathy phenotype between Latinos and Blacks. *J. Diabet. Complicat.* 2009;23(6):371–375. https://doi.org/10.1016/j.jdiacomp.2008.05.001.
10. Smith JP, Cyr LG, Dowd LK, Duchin KS, Lenihan PA, Sprague J. The veterans affairs continuous positive airway pressure use and diabetic retinopathy study. *Optom Vis Sci.* 2019;96(11):874–878. https://doi.org/10.1097/OPX.0000000000001446.
11. Tejero-Garcés G, Ascaso FJ, Casas P, et al. Assessment of the effectiveness of obstructive sleep apnea treatment using optical coherence tomography to evaluate retinal findings. *J Clin Med.* 2022;11(3):815. https://doi.org/10.3390/jcm11030815.