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"Glaucomatous fields" after monthly intravitreal injections: Normal tension glaucoma or a mimicker?

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ABSTRACT

Purpose: Anti-vascular endothelial growth factor (VEGF) injections, while used to effectively treat numerous retinal vascular conditions, can be associated with transient and prolonged ocular hypertension. There is minimal literature detailing the development of normal-tension glaucoma (NTG) following intravitreal anti-VEGF injections.

Observations: A 38-year-old Caucasian male with no medical or ocular history was diagnosed with an inferior HRVO with macular edema in the left eye. The patient received a total of eleven monthly intravitreal aflibercept injections over one year, with maintenance of stable vision and intraocular pressure (IOP) throughout the treatment period and during follow-up. Nine months after the last aflibercept injection, cup-to-disc asymmetry, inferior thinning of retinal nerve fiber layer (RNFL), and reduced superior visual field was evident in the left eye. Clinically, the patient was consistent with normal tension glaucoma and thus, the patient was started on daily timolol drops; however, the role of the glaucomatous findings being secondary to repeated injection-related IOP elevations is possible.

Conclusions and Importance: While the clinical features based on visual fields and RNFL thinning with unmedicated normotensive IOP may suggest NTG in a patient, this clinical presentation may be a masquerader of NTG with the etiology of the glaucoma optic neuropathy caused by cumulative impact of transient IOP elevations secondary to intravitreal injections.

1. Introduction

Although an effective treatment for various retinal vascular diseases, anti-vascular endothelial growth factor (VEGF) injections are associated with transient elevations in intraocular pressure (IOP)[1] and persistent ocular hypertension leading to glaucoma.[2,3] Limited prior literature has studied the association between hemi-retinal vein occlusion (HRVO) and glaucoma, with an enlarged cup-to-disc ratio suspected to compromise retinal venous return in the untimely clinical setting.[4,5] However, we describe the development of delayed optic nerve cupping and clinical features mimicking normal-tension glaucoma (NTG) following intravitreal aflibercept injections as HRVO treatment.

1.1. Case report

A 38-year-old Caucasian male was diagnosed with an inferior HRVO (Fig. 1a and b) with macular edema in the left eye (Fig. 2a). Visual acuity (VA) was 20/50 and IOP was 15 mmHg in the left eye (VA 20/20, IOP 15 mmHg OD) with unremarkable medical and ocular history. Systemic evaluation for hypercoagulable states as well as a complete blood count (CBC) with differential, erythrocyte sedimentation rate, and lipid profile was normal.

The patient was enrolled in the SCORE 2 study[6] and received monthly intravitreal aflibercept (2.0 mg/0.05mL; Eylea, Regeneron Pharmaceuticals, Tarrytown, NY) in his left eye for six months. Visual acuity, IOP, ophthalmoscopic examination, and spectral domain optical coherence tomography (SD-OCT) were performed at each monthly visit. After the first aflibercept injection, his VA improved to 20/20 with reduced macular edema. The patient received five more monthly aflibercept injections per the study protocol, followed by an additional five aflibercept injections over the following six months. There were no ocular or systemic adverse events. Subsequent to the eleven anti-VEGF injections, the patient was evaluated every three to four months with OCT. He maintained VA of 20/20-20/25 with normal IOP ranging

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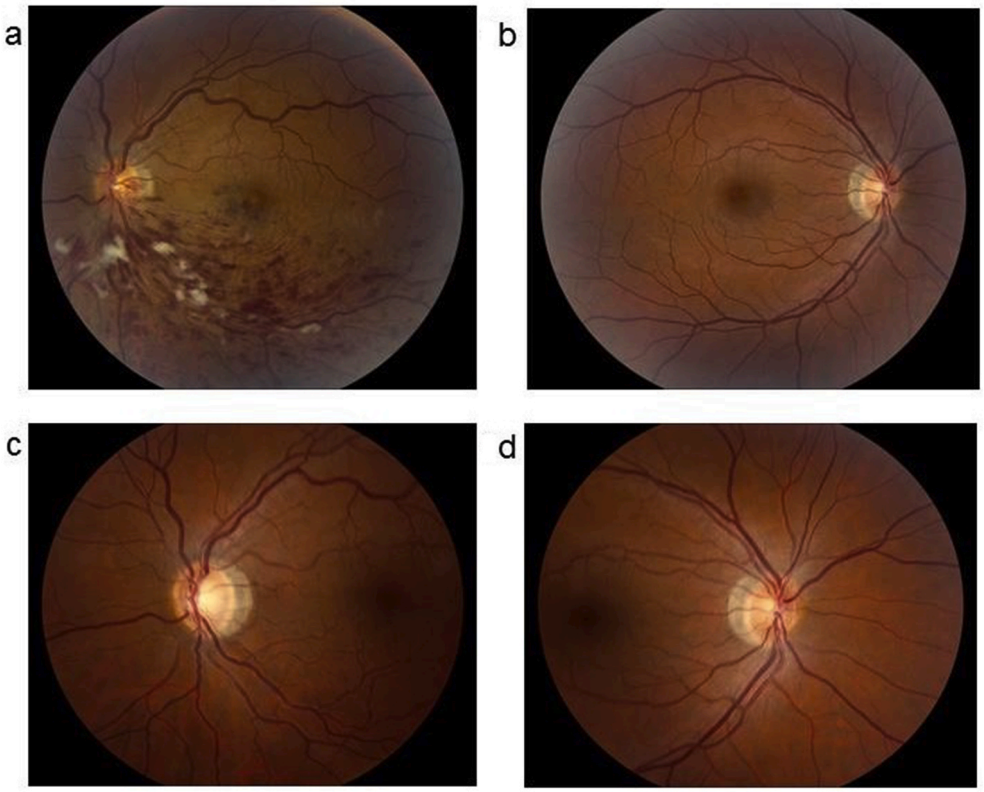

Fig. 1. a) Fundus photo of the left eye at presentation demonstrating inferior hemispheric retinal hemorrhages and cotton wool spots. b) Fundus photo of the right eye showing a cup-to-disc ratio around 0.3 with no evidence of glaucomatous discs. c) Fundus photo of the left eye nine months after presentation showing an enlarged cup-to-disc ratio but no retinal hemorrhages. d) Fundus photo of the right eye showing consistent cup-to-disc ratio of 0.3.

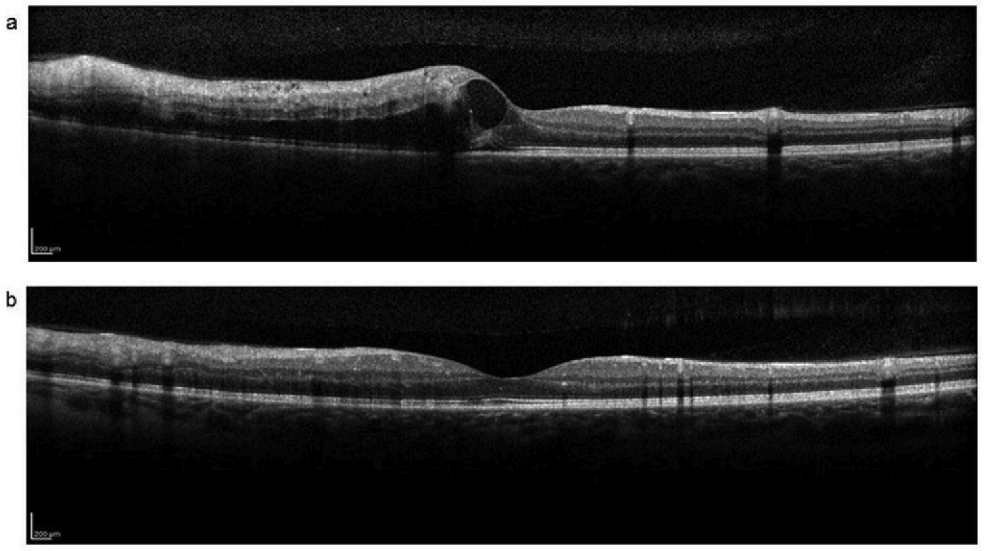

Fig. 2. a) SD-OCT at presentation revealing inner retinal hyper-reflective thickening as well as cystoid macular edema. b) SD-OCT shows normalization of the inner retinal hyperreflective thickening and no recurrence of cystoid macular edema.

between 12 and 18 mmHg OS, no macular edema (Fig. 2b), and no need for any further anti-VEGF or steroid injections.

Nine months after the final aflibercept injection, a larger cup-to-disc ratio (Fig. 1c and d) in the treated left eye was evaluated by retinal nerve fiber layer (RNFL) OCT (Carl Zeiss Meditec, Dublin, CA, USA), which showed thinning inferiorly (Fig. 3a). The patient was bilaterally myopic with a manifest refraction of −4.00D (diopter) sph/+2.25D cyl × 078° axis OD and −5.00D sph/+2.50D cyl x 104° axis OS. Pachymetry was 572 μm. Gonioscopy revealed a normal angle with no evidence of peripheral anterior synechiae or angle neovascularization. Examination otherwise remained stable with VA of 20/20 and normal IOP (17 mmHg OS, 14 mmHg OD). Funduscopic examination and OCT did not reveal retinal hemorrhages or macular edema. A Humphrey 24–2 visual field (VF) study (Carl Zeiss Meditec, Dublin, CA) demonstrated scattered spots depressed superiorly in the left eye (Fig. 3b). No abnormalities on RNFL-OCT or VF defects were identified in the right eye. Repeat CBC did

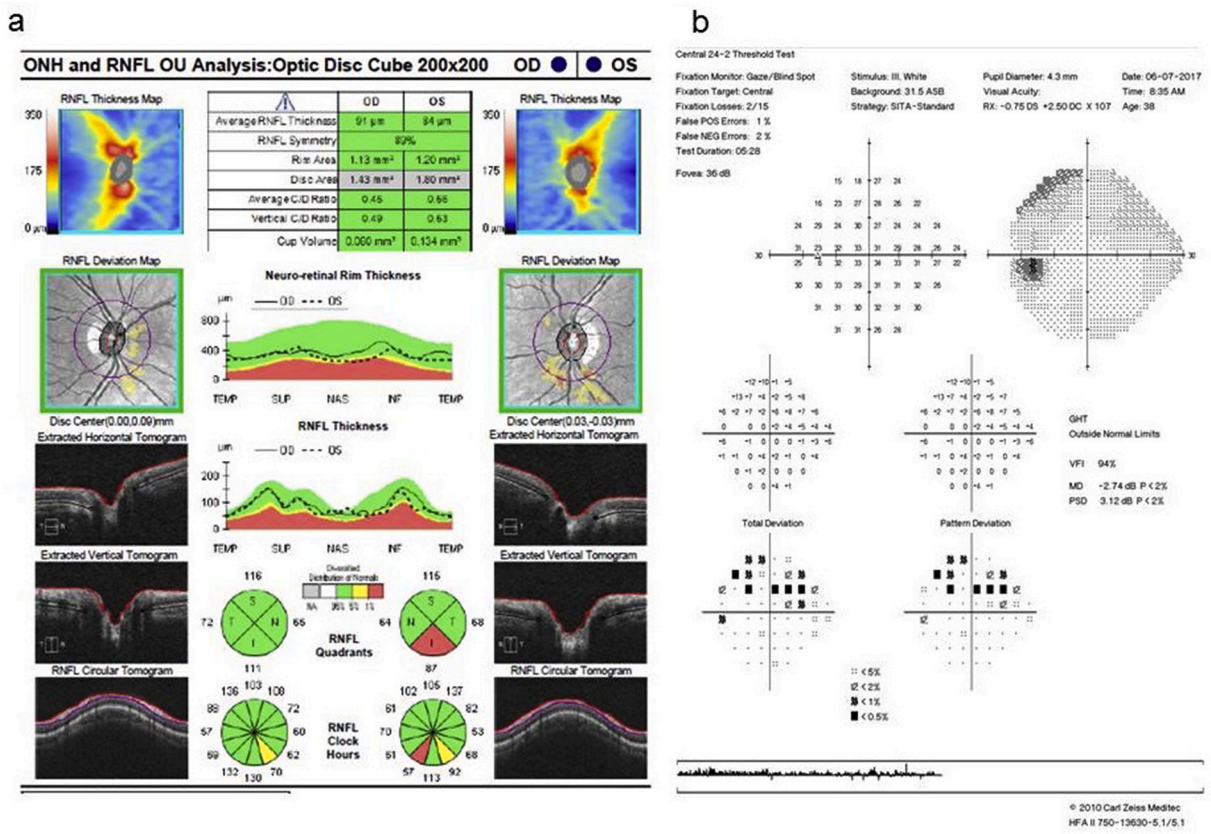

Fig. 3. a) Zeiss RNFL-OCT suggesting elongation of the cup and thinning of the inferior RNFL in the left eye (OD thickness 91 μm, OS thickness 84 μm). b) Humphrey 24–2 visual field revealed scattered spots depressed superiorly in the left eye.

not demonstrate any anemia and there were no other modifiable risk factors for normal-tension glaucoma (steroid use, obstructive sleep apnea, use of anti-hypertensive medications). Magnetic resonance imaging of the head and orbit were performed and did not reveal any orbital or intracranial processes. The patient was started on topical Timolol daily in the left eye with follow-up every three months. Twenty-two months after the last anti-VEGF injection, mild progression of the superior arcuate in the left eye was noted on the Humphrey 24-2 VF. Mean deviation slightly worsened from −2.74 dB to −4.97 dB and inferior RNFL thickness was now 82 μm (compared to 87 μm previously). Due to the noted progression, Timolol was increased to twice daily dosing with no further progression thus far and IOP continuing to remain in the mid-teens.

2. Discussions and conclusions

This case describes the development of delayed optic nerve cupping and clinical features consistent with normal-tension glaucoma in a patient that received multiple intravitreal aflibercept injections for treatment of macular edema related to HRVO. The patient had no documented persistent elevation of IOP over the three year follow-up period, yet developed a superior VF defect and inferior RNFL thinning in the treated eye. While the superior defect could have been related to the prior inferior HRVO, the corresponding inferior RNFL thinning is more consistent with glaucomatous VF loss. Accumulated impact from recurrent transient IOP elevations related to repeated intravitreal injections could also have contributed to the development of glaucomatous optic nerve damage and VF loss.[7] However, in the clinic setting, the occurrence of progressive optic neuropathy despite non-medicated IOP of less than 22 mmHg in a patient with myopia raises concern for NTG. Hence, similar to other conditions such as a brain mass, optic neuritis, optic nerve drusen, or steroid-induced glaucoma that may mimic and present as NTG,[8] it is important to note that injection-related transient repeated IOP elevation can masquerade as NTG as well.

Additionally, glaucoma itself is a well-known risk factor of retinal vein occlusions.[9] In our patient, we do not have RNFL or VF testing of the left eye prior to the development of the HRVO, and thus pre-existing glaucomatous changes, cannot fully be excluded. However, unremarkable RNFL and VF in the right (non-intervened) eye may suggest lack of preexisting glaucoma. Ischemic damage secondary to the cotton wool spots and retinal hemorrhages visualized in Fig. 1 itself could also contribute to thinning of the superficial retinal layers and optic fibers seen in our patient.[5] However, the RNFL thinning visualized in Fig. 2a cannot solely be attributed to the ischemic damage since corresponding visual field defects in the superior arcade indicative of possible glaucomatous disease were also evident in our patient.

Large randomized trials support prompt and regular anti-VEGF injections for RVO with macular edema.[10] However, the stabilization in VA and resolution of macular edema with six aflibercept injections in this patient raises an important question regarding the role of treating and observing patients who maintain excellent visual and anatomic outcomes. Structural changes in the optic nerve and RNFL thinning despite unmedicated normotensive IOP as in our patient is clinically consistent with NTG. However, when these findings occur in a patient receiving repeated intravitreal injections, it is possible that the NTG is masquerading cumulative damage secondary to injection-related transient IOP elevations. Long-term monitoring of the optic nerve and macula in patients treated with serial anti-VEGF may be advised since glaucomatous structural changes can develop despite normal IOP.

Patient consent

Consent for publication: Ethical approval and consent was obtained from the patient for publication of this case.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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3. Final approval of the version to be published; AND.

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of competing interest

Dr. Bakri has served as a consultant for Allergan, Genentech, Novartis and Zeiss. No financial disclosures for all other authors. All authors have no conflicts of interests.

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