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Acute macular neuroretinopathy associated with intravitreal anti-VEGF injection: A case report

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ABSTRACT

Purpose: to report a case of acute macular neuroretinopathy occurring after intravitreal aflibercept injection for macular edema due to CRVO.
Observations: Two days after Aflibercept intravitreal injection, the patient developed vision loss associated with a central scotoma. Optical coherence tomography showed a hyperreflective band at the level of the outer nuclear/outer plexiform layer corresponding to the patient's scotoma, ruling in the diagnosis of acute macular neuroretinopahty. Even though the OCT abnormalities resolved spontaneously, only partial resolution of the scotoma was observed 4 months later.
Conclusions and importance: Acute macular neuroretinopathy might be associated with intravitreal anti-VEGF injection.

1. Introduction

Acute macular neuroretinopathy (AMN) was initially described in 1975 in four young women on oral contraceptives who presented with sudden decreased vision and scotomas and had characteristic wedge-shaped dark macular lesions on fundus exam.[1] Although these lesions were initially proposed to be in the superficial retina, the advent of optical coherence tomography (OCT) allowed better delineation of the retinal anatomy. The Fourier-domain OCT with better resolution than time-domain OCT (TD-OCT) showed hyperreflective lesions at the level of the outer nuclear and plexiform layers.[2] More recently, projection-resolved optical coherence tomography angiography (PR-OCTA) showed decreased deep capillary plexus flow in AMN proposing an explanation for its vascular etiology.[3]

AMN typically affects young women and is associated with a broad range of vaso-occlusive risk factors including flulike illnesses, oral contraception, sympathomimetics use, and shock. AMN has also been reported after non-ocular trauma, cataract surgery[4] and Covid-19 infection.[5] One case of AMN was described following ranibizumab intravitreal injection in a diabetic patient and another case following aflibercept injection for central retinal vein occlusion (CRVO).[6,7] To our knowledge, we report the second case of AMN after Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc) intravitreal (IVT) injection for CRVO-related macular edema.

2. Case report

A 48-year-old man presented to us 5 days after an IVT injection of aflibercept for macular edema associated with CRVO. He developed vision loss in the right eye 2 days following the injection. This was his fourth intravitreal injection for CRVO-related macular edema. He is known to have mild to moderate glaucoma for which he uses dorzolamide/timolol and brimonidine. He also has type 2 diabetes mellitus without diabetic retinopathy and no other systemic diseases.

On examination, best-corrected visual acuity was 20/150 (down from 20/80 prior to the injection) in the right eye and 20/25 in the left eye. Intraocular pressure and anterior segment examination were within normal limits in both eyes except for a posterior chamber intra-ocular lens in the right eye. Dilated fundoscopic examination and color fundus photography revealed blunting of the foveal reflex with pan-retinal photocoagulation scars in the right eye. On 10-2 Humphrey visual field examination, a visual field defect was noted centrally in the right eye (Fig. 1). Fluorescein angiography (FA) showed delayed venous

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Abbreviations

AMN	Acute macular neuroretinopathy
OCT	optical coherence tomography
TD-OCT	time-domain optical coherence tomography
PR-OCTA	projection-resolved optical coherence tomography angiography
CRVO	central retinal vein occlusion
SD-OCT	Spectral domain optical coherence tomography
FA	Fluorescein angiography
OPL:	outer plexiform layer
ONL:	outer nuclear layer
EDI-OCT	enhanced depth imaging OCT
VEGF	vascular endothelial growth factor

filling in the right eye attributable to CRVO but no significant macular pathology (Fig. 2). Compared to initial imaging prior to the injection, spectral domain OCT (SD-OCT) demonstrated resolving macular edema with a highly reflective band at the level of the outer nuclear layer/outer plexiform layer on both sides of the fovea but mainly nasally with disruption to the ellipsoid and interdigitation zones (Fig. 3). En-face imaging of the DCP showed increased reflectivity in the perifoveal area. This was best seen on a 40-μm thick slab located subjacent to the outer plexiform layer (offset anterior to Bruch's membrane 117 and 77 μm) (Fig. 3). However, there was no detectable corresponding capillary flow deficit on OCTA (Fig. 3). The findings were consistent with an acute AMN lesion.

On follow up 2 weeks and 4 months later, partial but significant progressive resolution of the central scotoma was noted both subjectively and objectively on visual field examination (Fig. 1). SD-OCT showed resolution of the hyperreflective band with restoration of the ellipsoid and interdigitation zones by 4 months. However, there was corresponding thinning of the outer nuclear layer (ONL) of the retina (Fig. 3) accompanied by a significant decrease in hyperreflective lesions previously found on en-face imaging.

OCTA did not show any flow deficit at the level of the choriocapillaris corresponding to the AMN lesion at any time point during follow up (Fig. 3).

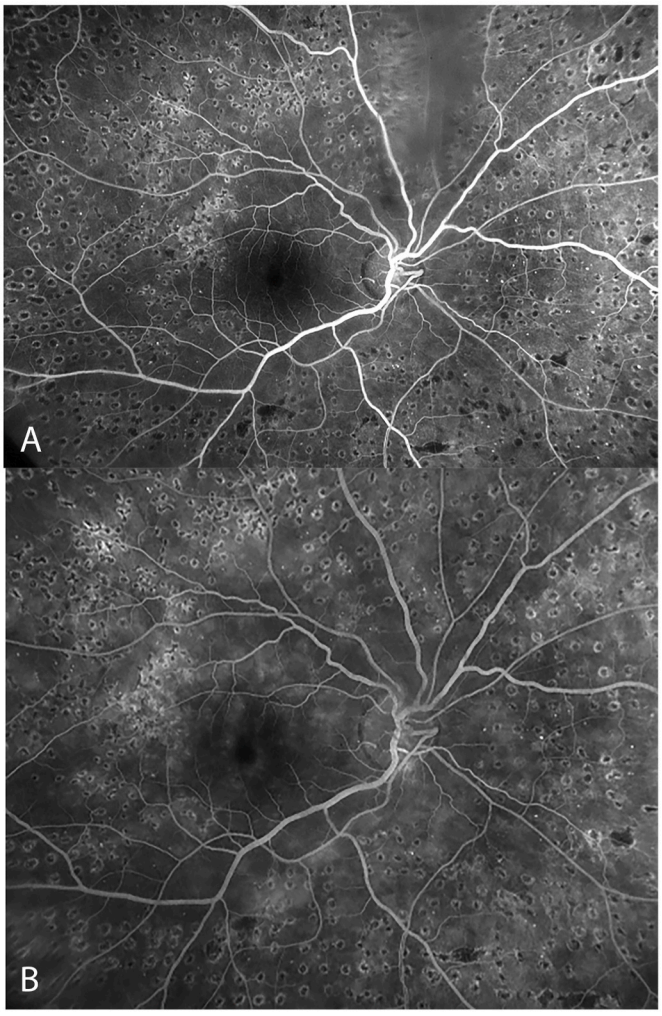

Fig. 2. Mid (A) and late (B) fluorescein angiography frames of the right eye showing old panretinal photocoagulation scars and a relatively unremarkable macular area except for mild late hyperfluorescence in the parafoveal area and in the superior macula (B).

3. Discussion

To our knowledge, the case illustrated here represents the second report of AMN following intravitreal injection of aflibercept,[7] and the third to be reported following anti-VEGF injection in general.[6] Although the fundus image of our patient did not show the typical lesion of AMN, SD-OCT showed the pathognomonic hyperreflective OPL/ONL lesion with disruption of ellipsoid and interdigitation zones. En-face OCTA also showed hyperreflective perifoveal lesions at the level of the DCP as previously reported.[2–4]

AMN is a rare entity classically presenting with a reddish-brown, wedge-shaped macular lesion the apex of which usually points towards the fovea.[1] The exact pathophysiology of AMN is still under research. An underlying disruption in the DCP seems to be the most accepted theory.[4] Multi-modal imaging including near infrared

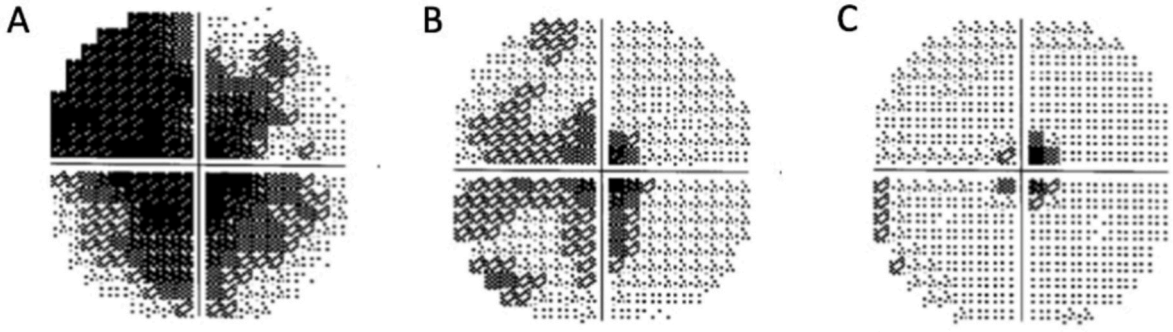

Fig. 1. 10-2 Humphrey visual field test of the right eye showing the central scotoma at baseline (A) with its progressive incomplete resolution 2 weeks later (B) and up to 4 months following presentation (C).

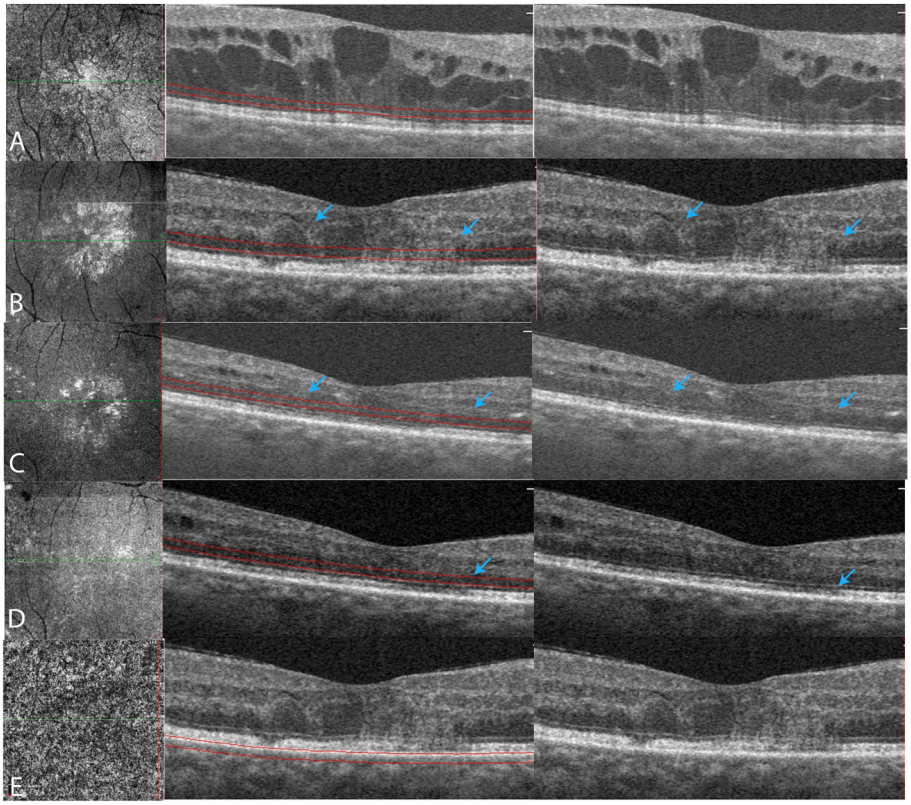

Fig. 3. Optical coherence tomography angiography en face c-scans (left column), corresponding OCT b-scans (middle column) and corresponding 40-μm thick slab subjacent to the outer plexiform layer (right column) of the patient's right eye (A-E). (A) Prior to the last aflibercept injection, c-scan showing diffuse cystoid macular edema with absence of the AMN lesions. (B) Following the injection at presentation with visual loss, c-scan showing perifoveal hyperreflective lesions. The corresponding b-scan showing hyperreflective bands affecting the OPL and ONL on both sides of the fovea, more prominent nasally (blue arrows). Note the disruption to the ellipsoid and interdigitation zones. (C) 2 weeks later, c-scan showing a decrease in the hyperreflectivity of the lesions. Corresponding b-scan showing also decreased reflectivity of the OPL and ONL (blue arrows). (D) at 4 months follow up, c-scan showing significant decrease in the hyperreflective lesions. Corresponding b-scan showing thinning of the ONL. Also note restoration of the ellipsoid and interdigitation zones (blue arrows). (E) Choriocappillaries slab at presentation showing no flow deficit corresponding to the AMN lesion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

reflectance, SD-OCT and projection-resolved OCTA has helped better characterize these lesions. Cross-sectional PR-OCTA was used by Chu et al. in order to detect the site of blood flow alteration in the retinal microvasculature in AMN. The study showed that AMN is associated with decreased DCP flow signal.[3] Recently, using OCTA, Lee et al. found a flow deficit at the level of the choriocapillaris corresponding to the AMN lesions in all 9 eyes studied.[8] Another report by Hashimoto et al. suggested, using enhanced depth imaging OCT (EDI-OCT), choroidal involvement in the pathogenesis of AMN. They reported that the morphological and circulatory patterns of the choroid in their patient was similar to those of choroiditis-causing conditions, pointing towards an inflammatory role in the pathogenesis of AMN causing circulatory disturbance in ocular microvasculature.[9] However, in our case we did not find any choroidal nonperfusion corresponding to the AMN lesion on OCTA. Therefore, the findings in our case lend support to the theory of DCP, rather than choriocapillaris, involvement in the pathogenesis of AMN.

Wheatly and Sarraf reported the first case of AMN in a diabetic patient 3 days following Ranibizumab injection.[6] Iovino et al. more recently associated another case of anti-VEGF injection with the occurrence of AMN in a case series describing coincident Paracentral acute middle maculopathy (PAMM) and AMN lesions. A patient in this case series developed AMN one week after Aflibercept IVT injection in the right eye.[7] In our report we describe another AMN case shortly after Aflibercept injection. These 3 cases together highlight the temporal association between IVT injection and AMN and underscore the need to further investigate the relationship between the two events in larger studies.

We speculate that there are three possible explanations underlying the acute occurrence of AMN post anti-VEGF injections; one is a sudden increase in the intraocular pressure post injection that might affect blood flow in the precapillary arterioles of the DCP. This has been previously suggested by Sarraf et al.[6] Another possible explanation is a subclinical intraocular inflammation caused by the procedure. An ocular small vessel vasculitis and subsequent ischemia could have contributed to this entity. This is endorsed by the report of Hashimoto et al. who suggest an underlying inflammation to be the cause of AMN.[9] The third possible explanation can be related to the effect of the blockade of vascular endothelial growth factor (VEGF). Since VEGFs are vasodilators, their antagonism might lead to a decrease in the caliber of retinal vessels with resultant decreased flow in retinal capillaries and subsequent ischemia.[10]

AMN was also recently reported in association with several diseases such as leukemia, ulcerative colitis and chronic kidney disease, all of which can cause anemia and thrombocytopenia with potential subsequent hypoxia.[11] Our patient also had a history of diabetes and CRVO. Both are risk factors for vascular insufficiency, which may have contributed to hypoxia and the development of AMN. Nevertheless, we believe that the Anti-VEGF IVT injection may be an important contributor to the AMN lesion development due the close temporal relation and the growing evidence with two previous similar reports.

4. Conclusion

We report a unique case of AMN following IVT Aflibercept injection in a diabetic patient with a history of CRVO-associated macular edema. While anti-VEGF injections are indispensable for the treatment of many serious ocular pathologies, this case highlights a potential rare additional side effect of this treatment modality. Further investigation is needed to confirm causality and risk factors for developing AMN following intravitreal injections. Clinicians are encouraged to carefully look for AMN in patients with visual changes following administration of intravitreal anti-VEGF and to elicit a history of recent intravitreal injection in patients presenting with AMN.

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Authorship

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

Patient consent

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

Declaration of competing interest

All authors have no financial disclosures.

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