

A rare case of occlusive juxtafoveal retinal telangiectasias associated with lesions of the central nervous system: A cerebroretinal vasculopathy like phenotype without mutations in the TREX1 gene

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ABSTRACT

Purpose: To report a rare case of bilateral occlusive juxtafoveal retinal telangiectasias associated with central nervous system lesions and renal impairment.

Observations: A 47-year-old woman presented to clinic with subjective vision loss in the right eye with best-corrected visual acuity (BCVA) 20/80. Fundoscopic examination, fluorescein angiography (FA), and optical coherence tomography with adjunct angiography (OCT/OCT-A) revealed macular microhemorrhages, enlarged foveal avascular zones (FAZ), and occlusive juxtafoveal telangiectasis with pruning of the macular capillaries in both eyes. Patient subsequently developed memory loss, dizziness, nystagmus, and diplopia secondary to intermittent exotropia. She was found to have a two-millimeter aneurysm of the proximal posterior cerebellar artery along with several scattered white matter changes on brain magnetic resonance imaging (MRI). Genetic workup revealed no mutations in the TREX1 gene. With continued surveillance over 18 months, the patient's BCVA deteriorated to 20/200 OU and she developed mild renal impairment, without further CNS complications.

Conclusion and importance: Patients who present with vision loss secondary to occlusive juxtafoveal telangiectasias should undergo imaging of the central nervous system (CNS) for architectural abnormalities in cerebral vasculature and white matter. Further investigation of patients with the Gass-Blodi type 3 macular telangiectasia – cerebroretinal vasculopathy phenotype is required to optimize management protocols for both retinal and CNS lesions. At this time, no interventions have demonstrated clear benefit in vision preservation or recovery.

1. Introduction

The significance of retinal telangiectasis involving the macula as a cause of progressive vision loss was first established in 1956 and was proposed to represent various manifestations of Coats' disease.¹ Gass later utilized fluorescein angiography and meticulous fundoscopic biomicroscopy to elucidate idiopathic juxtafoveal telangiectasia (IJT) as a unique disease entity that could be subdivided into three major divisions, each with two subclasses (A and B).^{2,3} In 1993, Gass and Blodi released an updated classification schema for IJT.³ Only seven patients met the criteria for IJT type 3, which was described as the occlusive subtype.³ Patients in this category also had systemic diseases such as gouty arthritis, ulcerative colitis, and polycythemia. A specific subset of

type 3 patients displayed hyperactive deep tendon reflexes along with small central nervous system (CNS) white matter lesions and frontoparietal lobe pseudotumors characterized by fibrinoid necrosis.²⁻⁴ These patients were classified as IJT type 3B.³

In 2006, Yanuzzi and Blodi sought to simplify the idiopathic macular telangiectasia classification and utilized optical coherence tomography (OCT) to support their revision.⁵ The authors suggested that the occlusive subtype shared extensive clinical overlap with cerebroretinal vasculopathy (CRV), an autosomal dominant disorder, first reported by Grand et al. CRV and several other hereditary oculocerebral syndromes were found to be related to mutations in TREX1, a gene that encodes an essential 3'-5' DNA exonuclease.⁶ Several known mutations in TREX1 have demonstrated downstream effects on autoimmunity, endothelium

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homeostasis, and vascular aging caused by oxidative stress.⁶⁻⁹

Herein, we report a case of bilateral occlusive juxtafoveal retinal telangiectasia associated with CNS lesions and renal impairment, which falls within the Gass-Blodi IJT type 3 – cerebroretinal vasculopathy phenotype. Multimodal imaging and genetic testing for TREX1 mutations were utilized to provide valuable insight into this rare disease process.

2. Case report

A 47-year-old woman presented with complaints of new floaters in the right eye associated with subjective worsening of visual acuity and mild ocular discomfort. Her past ocular history was significant for mild myopia. The patient was asymptomatic in the left eye. Her pertinent medical history included depression, hyperlipidemia, medication controlled hypertension with systolic pressures ranging from 120 to 140s and diastolic pressures ranging from mid 70s–80s per chart review since 2013, and atrial fibrillation. The patient was taking atorvastatin, lisinopril, extended release metoprolol succinate, pantoprazole, and sertraline to treat her underlying medical conditions. She was a current smoker with a 20 pack-year history. Best-corrected visual acuity (BCVA) was 20/60 with correction $-1+0.75 \times 23$ in the right eye and 20/60 with -1 in the left eye.

Fundoscopy examination in the right eye revealed a well barricaded retinal tear with resolving vitreous hemorrhage; no new retinal tears were noted. Several micro hemorrhages were observed within the macula of both eyes.

Fluorescein angiography (FA) demonstrated juxtafoveal retinal capillary occlusions with circumferential foveal capillary dropout, most prominent in the temporal parafoveal (Fig. 1). Dilated capillary terminals and telangiectatic vessels were appreciated within the early FA arteriovenous filling phase (Fig. 1A). Hyperfluorescence and mild fluorescein leakage was noted within both eyes on late-phase FA; the hyperfluorescence was most prominent in the areas of parafoveal telangiectasis (Fig. 1B and C). The left eye also contained a conspicuous telangiectatic venule, which appeared to bisect the temporal aspect of the FAZ (Fig. 1C).

Heidelberg Spectralis optical coherence tomography (OCT) revealed thinning and disorganization of the retinal inner layers (DRIL) in both eyes (Fig. 2A and B). The DRIL was most prominent within the temporal parafovea in both eyes. The outer retinal layers and RPE; however, had no architectural abnormalities (Fig. 2). En face images taken at the level of the superficial capillary plexus revealed flow voids concentrated around the telangiectatic vessels (Fig. 4C and D). The deep capillary plexus also demonstrated significant juxtafoveal capillary dropout within both eyes (Fig. 4E and F). Although BCVA was better in the left eye, more prominent flow voids within the superficial and deep capillary plexuses were demonstrated (Fig. 4D and F).

Over the course of the next 7 months, the patient developed worsening memory, dizziness, intermittent horizontal diplopia, and experienced repeated unprovoked ground-level falls. Magnetic resonance angiography (MRA) of the brain was performed and revealed a conspicuous 2-mm aneurysm of the proximal posterior cerebral artery (Fig. 5A). Further MRI sequencing demonstrated several scattered T2-weighted hyperintense lesions within the right frontotemporal lobe and left cerebellum (Fig. 5B and C). A comprehensive infectious and inflammatory work-up was initiated, which revealed only a mild polyclonal gammopathy and hypergammaglobulinemia, as seen in chronic inflammatory conditions. In collaboration with the rheumatology service, a thorough investigation revealed no evidence of a systemic inflammatory or autoimmune process. Lastly, the patient's renal function began to decline as evidenced by an elevated creatinine of 1.11mg/dl, up from her baseline of 0.75mg/dl (normal limits 0.49–1.10mg/dl), and depressed glomerular filtration rate (GFR).

The patient's constellation of symptoms and clinical findings became concerning for cerebroretinal vasculopathy, and several other

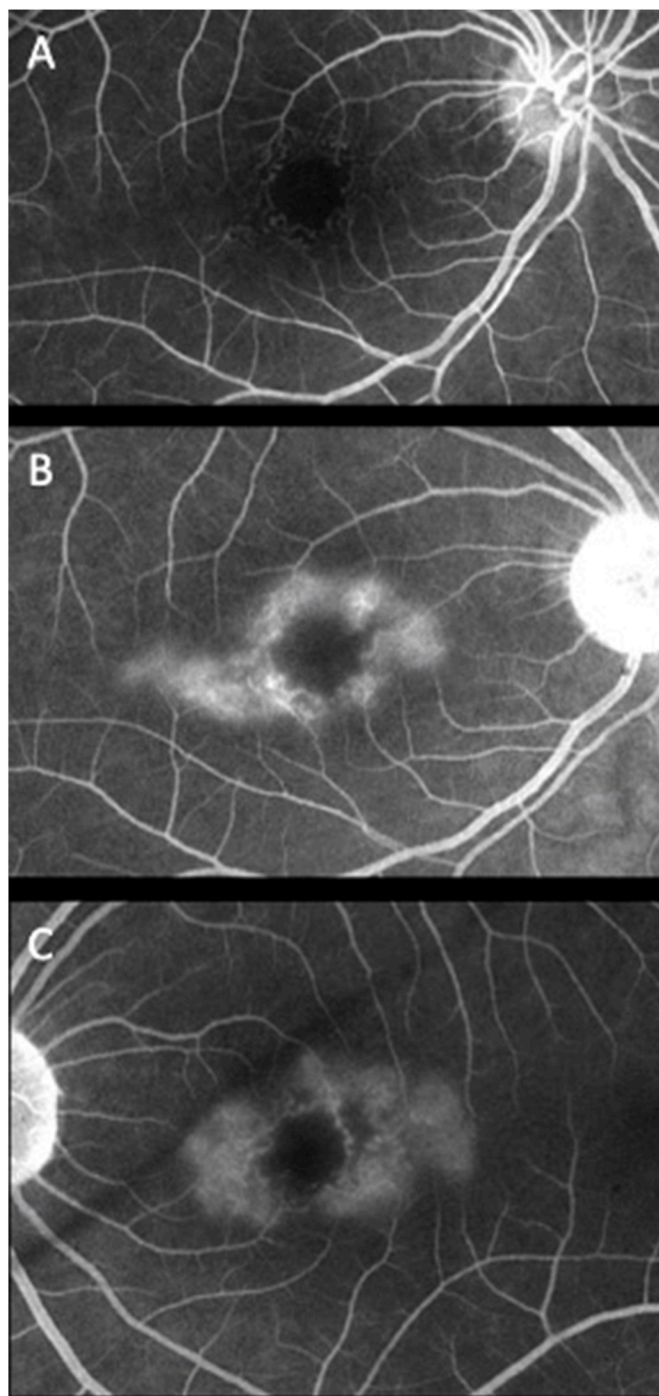


Fig. 1. Early-phase fluorescein angiography (FA) of the right eye revealed circumferential capillary dropout creating a grossly enlarged appearing FAZ A) Late-phase FA demonstrated mild fluorescein leakage with prominent focal hyperfluorescence noted in areas containing telangiectatic vessels B) Late-phase FA of the left eye also showed circumferential parafoveal hyperfluorescence with many telangiectatic vessels clearly evident C).

oculocerebral syndromes, which are associated with mutations in the TREX1 gene. Molecular diagnostic testing was provided by Foundation for Fighting Blindness initiative with Blueprint Genetics (My Retina Tracker Panel Plus). The panel scrutinized 266 genes and 4318 exons for mutations implicated in inherited retinal disease (IRD). No mutations were found in the patient's TREX1 gene. A heterozygous pathogenic frameshift variant in KIAA0586 (c.428del,p.(Arg143Lysfs*4) was detected, insufficient to cause disease.

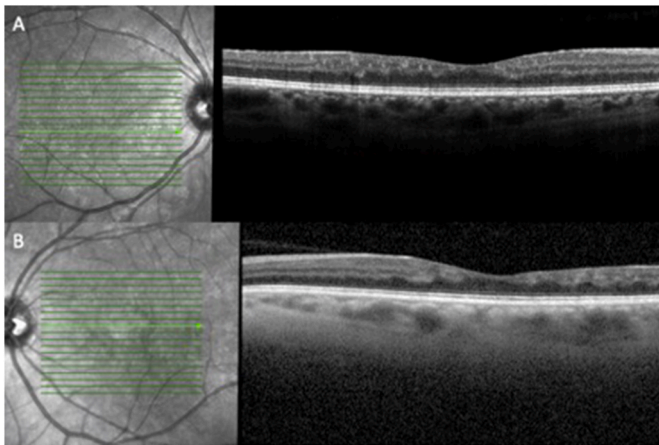


Fig. 2. B scans of the macula were obtained with Heidelberg Spectralis optical coherence tomography (OCT) and revealed disorganization of the retinal inner layers (DRIL) of the right eye A) and left eye B). In both eyes the DRIL was more prominent within the temporal parafovea, which corresponded to the areas of occlusive telangiectasis. The outer retinal layers and retinal pigment epithelium appeared intact in both eyes.

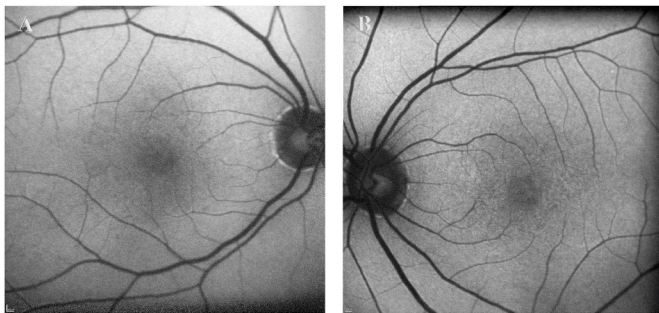


Fig. 3. Fundus autofluorescence demonstrated mildly reduced foveal autofluorescence within the right eye A) and left eye B).

Due to leakage pattern in fluorescence angiography, intra-ocular pressures of 19 in the right eye and 21 in the left eye, mild optic nerve asymmetry, and few side effects, the patient was started on dorzolamide drops three times daily in both eyes. Despite this treatment, her vision continued to deteriorate. Unfortunately, eighteen months after her initial presentation, the patient’s BCVA had decreased to 20/200 in both eyes.

3. Discussion

IJT type 3B was first described by Gass and Blodi to describe central vision loss due to juxtafoveal capillary occlusion and telangiectasias without the contribution of lesion exudation.^{2,3} The presence of systemic diseases, hyperreflexia, and CNS white matter lesions was also noted in this subcategory.³

Prior reports relied heavily on fluorescein angiography and fundus photography to appreciate the parafoveal capillary dropout, enlarged FAZ, and juxtafoveal telangiectatic vessels associated with this disease.^{3,4,14} Our imaging is particularly similar to a report of cerebroretinal microangiopathy with occlusive telangiectasia by Choudhury et al., where a 14-year-old male was found to have an enlarged FAZ and extensive capillary dropout with parafoveal telangiectatic vessels on FA.¹⁵

In a similar fashion we were able to describe vision loss secondary to juxtafoveolar retinal capillary occlusions with circumferential foveal capillary dropout, most prominent in the temporal parafovea, visualized

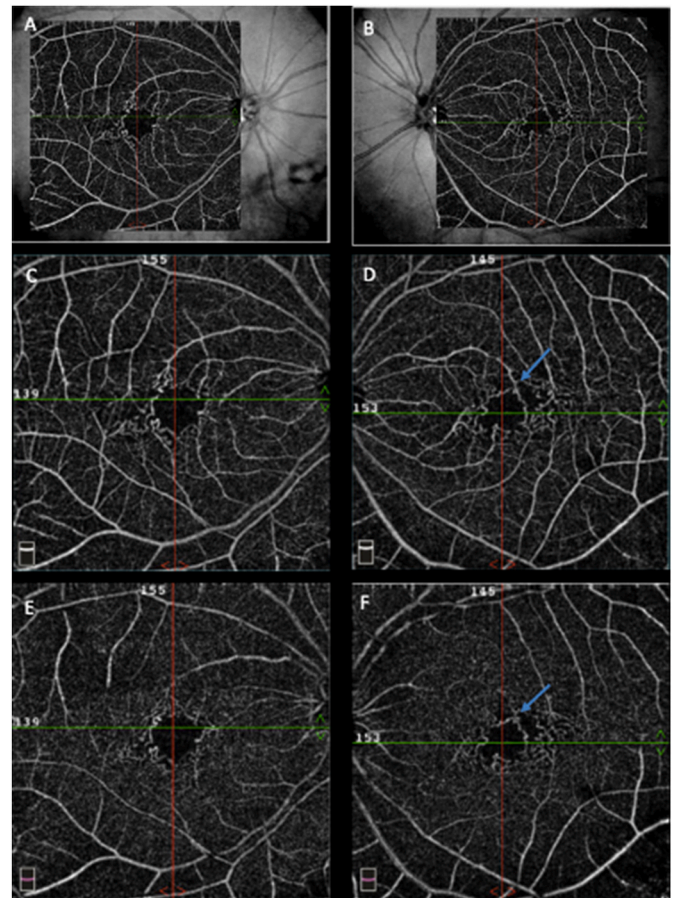


Fig. 4. 8 × 8 mm sections of the macula were imaged with optical coherence tomography angiography (OCT-A) (device - Optovue OCT, mode - HD Angio Retina-RTVue XR, algorithm version - A2017.0.0.16) to detect vascular alterations within the macula of the right eye A) and left eye B) En face imaging at the level of the superficial retinal capillary plexus revealed 360° parafoveal capillary dropout, a grossly enlarged foveal avascular zone (FAZ), and prominent telangiectatic vessels within the temporal and inferotemporal parafovea C) similar findings were observed with significant flow voids within the superficial capillary plexus of temporal parafovea of the left eye D) telangiectatic end capillaries and venules were seen in close proximity to deep capillary plexus flow voids, which appeared more prominent within the temporal parafovea than nasal parafovea in both the right eye E) and left eye F). The blue arrows seen in panels (D) and (F) highlight a venule with origin in the superficial capillary plexus that invades the FAZ and collapses into the deep capillary (F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

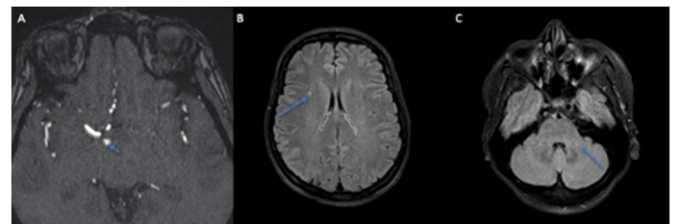


Fig. 5. Magnetic resonance angiography (MRA) and magnetic resonance imaging (MRI) sequences of the brain were obtained after the patient developed memory loss, persistent dizziness, nystagmus, intermittent horizontal diplopia, and had non-traumatic falls. MRA revealed a 2 mm aneurysm of the right posterior cerebral artery A) and scattered T2-weighted hyperintense lesions within the frontotemporal lobe white matter tracts B) and left cerebellum C).

on FA (Fig. 1). These findings, along with dilation of capillary terminals on the early FA arteriovenous filling phase (Fig. 1B,C), are consistent with suggestions from Yanuzzi and Blodi to view this disease process as an ischemic ocular manifestation of systemic or cerebral familial disease, rather than classify it under the umbrella of idiopathic macular telangiectasia.

Areas of juxtafoveal ischemia within the macula were again demonstrated by the presence of DRIL which was detected on the OCT B-scans within in each eye (Fig. 2A and B). To the best of our knowledge, prior reports on the CRV spectrum of disease either predated OCT or did not include OCT B-scans of the macula; however, DRIL length has been found to positively correlate with FAZ size in retinal vascular disease.¹⁶

Lastly, OCT angiography further demonstrated juxtafoveal capillary dropout which affected both the superficial and deep capillary plexuses (Fig. 4C–F). It is interesting to note that despite this extensive multilevel capillary dropout noted on multiple imaging modalities, the architecture of the photoreceptors remained intact (Fig. 2A,B). Furthermore, no pigmentary changes were noted on fundus autofluorescence (Fig. 3). While some of the patient's OCT angiography findings could possibly be related to her past history of hypertension (i.e. enlarged FAZ), she did not have typical funduscopic changes associated with hypertensive retinopathy such as retinal hemorrhages, retinal exudates, cotton wool spots, retinal edema, Elschnig spots or Siegrist streaks.

MRI findings subsequent to neurologic progression of disease revealed scattered T2-weighted hyperintense lesions within the right frontotemporal lobe and left cerebellum (Fig. 5B and C), highlighting the clinical overlap with CRV. Our radiographic findings aligned closely with those described Stam et al. who found that up 97% of patients with the CRV-phenotype had punctate lesions.¹⁷ Our patient's brain imaging did not reveal large rim-enhancing lesions or pseudotumors described by several authors^{4,7,11,13}; however, Stam et al. did find that several patients in their cohort had transformation of their punctate lesions, further highlighting the necessity for serial imaging.¹⁷

With continued follow up, the patient was noted to develop chronic kidney disease (CKD) stage 3; however, thorough work-up did not detect other systemic manifestations. While cerebroretinal vasculopathy is associated with the TREX1 gene, she had no genetic variants. The significance of TREX1 in terms of clinical outcomes was studied in three Dutch families with a history of cerebroretinal vasculopathy; family members carrying the mutation were found to have higher incidences of kidney disease, anemia, and Raynaud's phenomenon compared to their non-carrier relatives. None of the non-carriers reported any subjective visual loss.¹⁸

To date, there has been no association between mutations in KIAA0586 and occlusive juxtafoveal telangiectasis with cerebrovascular infarcts. Susac Syndrome was also considered within our differential given the patient's intermittent dizziness and episodes of falling; however, the patient lacked clinically significant hearing loss and larger-caliber retinal vasculature lacked any evidence of occlusion.²¹ Rheumatology's investigation was nonindicative of an inflammatory process, precluding steroids from the treatment regimen, consisting of dorzolamide drops and smoking cessation counseling. However, visual deterioration continued, and BCVA declined to 20/200 in both eyes eighteen months after initial presentation.

This decline in visual acuity as well as imaging findings are comparable to a case of retinal vasculopathy with cerebral leukodystrophy by Vodopivec et al., where visual acuity was reduced to 20/80 in the right eye and 20/50-1 in the left eye likely due to extensive retinal ischemia with enlargement of the foveal avascular zones, perivascular fluorescein leakage, hyperfluorescence of vessel walls and numerous scars from panretinal photocoagulation. Renal comorbidities were described in Vodopivec's report as well, as the patient was CKD stage 4 prior to management.²²

There is no known intervention that has demonstrated vision preservation at this time. Given the rarity of this disease, well established

guidelines for neuroradiologic imaging do not exist; however, we recommend early imaging of the brain via MRA and MRI for surveillance of CNS vasculopathy. Furthermore, serial imaging should be performed in the advent of focal neurologic deficits or other signs of clinical deterioration. Due to this case's unfavorable progression, and the limited means of intervention, further investigation is paramount for future understanding and management of patients with disease within the CRV phenotypic spectrum.

4. Conclusion

Patients presenting with central vision loss secondary to bilateral occlusive juxtafoveal retinal telangiectasias should undergo systemic workup, including imaging of the brain via MRA and MRI for surveillance of CNS vasculopathy and white matter lesions. OCT-A was useful in elucidating the vascular architecture of the macula in patients with the Gass-Blodi IJT type 3 – cerebroretinal vasculopathy phenotype. Further investigation of this rare disease process is required to optimize management regimens.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Conflicts of interest

The following authors have no financial disclosures: MPS, KHB, SKG, NMJ, BE, ML.

Authorship

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

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