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A Novel TREX1 Frameshift Variant (c.802del p.(Arg268Glyfs*9) Associated with Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations: a Case Report

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Case Report

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Abstract

Background: Report a Novel TREX1 Frameshift Variant (c.802del p. (Arg268Glyfs*9) associated with Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations (RVCL-S) and accompanying clinical features of the disease.

Case presentation:

A 42-year-old male with multiple substance abuse disorder presented to the emergency room in a state of confusion with worsening headaches. Neuroimaging (Computed Tomography scan/ Magnetic Resonance Imaging scan) was performed and brain mass with midline shift was noted. The differential diagnoses included brain abscess versus multiple sclerosis or mass lesion. Extensive workup did not confirm infection or demyelinating disease. Treatment with broad spectrum antibiotics yielded no benefit and brain biopsy showed inflammatory necrosis only. In addition to his brain lesions, peripheral neovascular retinopathy was found and treated with laser photocoagulation. He had a positive family history of retinal vasculopathy with cerebral leukodystrophy (RVCL) affecting father, paternal grandmother, and paternal cousins. Genetic testing showed a pathogenic TREX1 c.802del p. (Arg268Glyfs*9) variant. To our knowledge, this variant and its accompanying clinical features have not been previously reported.

Conclusions:

Retinal vasculopathy with cerebral leukodystrophy and systemic manifestations (RVCL-S) is a rare, autosomal dominant microangiopathy caused by truncating TREX 1 mutations, characterized by vascular retinopathy, neurological features, cognitive decline, Raynaud's phenomenon, anemia, and renal and hepatic involvement. The patient developed avascular necrosis of the femur. We describe clinical, ophthalmic, radiographic, and systemic features of this 42-year-old male with the novel TREX1 c.802del p. (Arg268Glyfs*9) variant with a review of the literature. Cerebral lesions with surrounding edema often require corticosteroid therapy and early recognition of RVCL-S may prevent unnecessary invasive procedures. There is no cure and patients are at risk for premature death. A genetic evaluation is essential to establish the diagnosis.

Background

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is a rare, autosomal dominant angiopathy affecting small arteries and capillaries, characterized by vascular retinopathy, neurological features, cognitive decline, and systemic features including Raynaud's phenomenon, anemia, and renal and hepatic disease[1]. First described in 1988 by Grand et al in an extended St. Louis family in eight family members over three generations who had retinal vasculopathy with central nervous system tumors and similar histopathology[2]. RVCL-S is caused by C-terminus truncating (frameshift or nonsense) mutations of three-prime-repair exonuclease 1 (TREX 1) on chromosome 3. Fewer than 15 pathogenic variants have been reported. Other names for this condition

are cerebroretinal vasculopathy (CRV), hereditary vascular retinopathy (HVR), hereditary systemic angiopathy (HSA), and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). The exact pathophysiology is not understood, but auto-inflammation is a proposed mechanism. TREX1 is normally anchored at the endoplasmic reticulum (ER) membrane and is outside the nucleus. However, in patients with RVCL, a mislocalized but active TREX1 3'-5' DNA exonuclease constitutively enters the nucleus and damages genomic DNA, leading to a syndrome of DNA damage, endotheliopathy, and inflammatory aging [3]. Genetic testing is required to establish the diagnosis.

The onset of symptoms of RVCL-S is typically between 30 to 50 years, of age with less than 44 families worldwide (less than 200 individuals) reported. Consideration of RVCL-S is important in the differential diagnosis of tumefactive CNS lesions. Clinical features at the initial presentation include skin involvement (Raynaud's phenomenon, vasculitis) in 40% of cases, visual impairment or asymptomatic retinopathy, and rapidly progressive neurological features after age 50, renal disease (30–50%), liver dysfunction (78%), hypertension, subclinical hypothyroidism (37%), anemia due to gastrointestinal bleeding, avascular necrosis of femoral head, and cardiomyopathy.

The TREX1 *c.802del p. (Arg268Glyfs*9)* variant in our patient is novel. This C-terminal frameshift at codon 268 is predicted to truncate the protein at approximately amino acid 276, resulting in loss of the transmembrane domain required for endoplasmic reticulum localization while preserving the catalytic exonuclease domain[4,6]. This mechanism is consistent with the pathophysiology of RVCL-S, in which mislocalized but enzymatically active TREX 1 leads to endothelial dysfunction and progressive vasculopathy. To our knowledge, this variant has not been previously reported, thereby expanding the mutational spectrum of RVCL-S.

This report characterizes the- clinical, ophthalmic, radiographic and genetic features, diagnostic evaluation, and emerging translational therapeutic approaches in a patient with RVCL-S caused by this novel TREX1 variant.

Case presentation

A 42-year-old Caucasian male presented to the emergency room with severe headaches, nausea, vomiting, and confusion after hitting his head on a truck. Computed Tomography scan (CT) revealed a left frontoparietal white matter lesion extending into the left basal ganglia and thalamic regions with vasogenic edema, mass effect, effacement of left lateral ventricle and a 6 mm rightward midline shift (Fig. 1A, B, C, D). He was diagnosed with acute encephalopathy secondary to the lesion and vasogenic edema.

Medical history was significant for tobacco use, opioid (Suboxone), cocaine, benzodiazepines, and cannabis use disorders. Blood culture remained negative. CT scan of the cervical spine showed only degenerative changes. Due to concern for malignancy, he underwent a left frontal craniotomy and lesion excision. Intraoperative pathology reported reactive changes in the brain parenchyma and a

macrophage-predominant inflammatory process with marked necrosis. Pathology report favored inflammation with concern for demyelination versus infection (Fig. 2A and B). The Neurosurgery tumor board concurred and favored diagnosis of abscess versus tumefactive necrosis (demyelination). Broad spectrum PCR test on the biopsy tissue was negative for specific microorganisms. CT Angiography showed no evidence of vasculitis or significant stenosis. Subsequent lumbar puncture noted Glucose 52 mg/dL, protein 38 mg/dL, 12 nucleated red blood cells/ µL with lymphocytic predominant. Antithrombin III, protein C, lupus anticoagulant, ACE, and lysozyme were elevated, indicating systemic inflammation.

Neuro-ophthalmic examination showed best-corrected visual acuity was 20/20 in both eyes with normal Ishihara color plate testing. Examination revealed mild temporal optic nerve pallor and peripheral retinopathy in the right eye, and peripheral avascular retina in the left eye (Fig. 3A and B). Humphrey visual fields showed inferior depression in both eyes (Fig. 4A and B), and optical coherence tomography (SD-OCT; Heidelberg Spectralis, Heidelberg, Germany) revealed retinal nerve fiber layer thinning with ganglion cell layer inferior-temporal wedge defects bilaterally (Fig. 5A, B, C and D). Fluorescein angiography (FA) (Optos plc, Dunfermline, UK) demonstrated bilateral peripheral neovascularization for which he was treated with laser photocoagulation (Fig. 6A and B). There was enlargement of the foveal avascular zone and macular leakage (Fig. 6B) which could be associated with occlusive telangiectasia (Gass-blodi type 3 telangiectasia). Further history revealed RVCL in his paternal grandmother, and paternal cousins and a father who died of “brain cancer” at age 38.

Comprehensive rheumatological evaluation was unrevealing but noted a positive lupus anticoagulant, and genetic testing consisting of a targeted variant testing– (buccal swab using Gene Dx Stamford, Connecticut, 06902, United States), identified a pathogenic TREX1 mutation (*c.802del p. (Arg268Glyfs*9*).

Discussion

We report a 42-year-old patient with RVCL-S harboring a novel TREX1 *c.802del p. (Arg268Glyfs*9*) frameshift variant, expanding the mutational spectrum of this rare disorder. He had Raynaud’s phenomenon, tumefactive cerebral lesions, cognitive decline, retinal neovascularization requiring photocoagulation and avascular necrosis of the left medial and lateral femoral condyle. An earlier recognition of RVCL-S would have prevented unnecessary brain surgery.

Impaired TREX1 nuclease activity causes the accumulation of DNA and micronuclei within the cytosol, leading to activation of the cGAS–STING pathway and a downstream type I interferon (IFN)-mediated inflammatory response[4]. In RVCL, however, the aberrant activity of the nuclear mislocalized TREX1 mutant causes DNA damage, leading to microvascular injury and the associated pathology.

Inflammatory tumefactive lesions with cerebral edema often respond to corticosteroids. Our patient's lupus anticoagulant positivity supports consideration of antiphospholipid antibody screening in RVCL-S, particularly in patients with thrombotic or atypical features, although evidence-based guidelines are lacking. Other important differentials diagnoses include Susac’s syndrome, cerebral autosomal dominant

arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Aicardi-Goutières syndrome (AGS) type 1, systemic lupus erythematosus susceptibility and familial chilblain lupus [4,16] but these considerations were eliminated by rheumatology lab testing and genetic testing.

Retinal vasculopathy with cerebral leukoencephalopathy (RVCL-S) can lead to premature death, with an average age of death at 53 years (SD 9.6, range 32-72 years), and an average life expectancy of 5-20 years after onset of symptoms[5, 6, 7]. Vascular retinopathy is noted to have telangiectasia, microaneurysms, cotton wool spots, perifoveal capillary obliterations and neovascularization, peripapillary nerve fiber layer thinning and reduced total macular volume. Other complications include secondary glaucoma and macular edema. Focal neurological dysfunction can be caused by intracerebral mass lesions, ischemic episodes that can present as classic lacunar syndromes, cognitive decline, migraines, epilepsy or psychiatric disturbances.

Classic radiographic features include white matter lesions at a young age that are T2-hyperintense with persistent nodular or rim enhancement with contrast and may be associated with diffusion restriction. These lesions may progress to space occupying lesions with vasogenic edema and displacing adjacent structures. The lesions are typically T2 hyperintense, T1 hypointense, and show ring enhancement with gadolinium, mostly in frontoparietal lobe [8, 9, 10]. Multiple cerebellar lesions, often bilateral and punctiform are also characteristic, particularly in advanced disease. Recent studies suggest that retinal OCT findings may serve as biomarkers for RVCL-S[1]. Decreased peripapillary retinal nerve fiber layer thickness, loss of total macular volume and thinning of inner plexiform layer are seen in TREX1 mutation carriers. Reduced neuroradiological cerebrovascular reactivity (CVR)[1], in both gray and white matter has also been identified as a biomarker of RVCL-S, while elevated Von Willebrand factor or, angiopoietin-2 are potential endothelial biomarkers[1]. Recently cerebral oxygen extraction fraction (OEF) has been studied as a marker for cerebral hypoxia-ischemia, elevated levels associated with progression in white matter hyperintensity and impairment in white matter microstructure, suggesting a role for tissue hypoxia-ischemia in underlying RVCL-S pathophysiology[11].

No specific disease modifying treatment is available. Various agents were tried with the goal of modifying autoimmunity, including corticosteroids, cyclophosphamide, methotrexate, chloroquine, azathioprine, IVIG and plasmapheresis yet no clear benefits were observed with these approaches.

Retinal neovascularization and macular edema should be treated with retinal laser photocoagulation and intravitreal anti-VEGF, respectively[12]. Cerebral lesions with surrounding edema should be treated with IV methylprednisolone followed by oral steroids. A case report has shown volumetric reduction of the brain lesion with small nodular enhancement [10].

Crizanlizumab has been investigated in phase II clinical trial for RVCL-S[13]. Preliminary results showed decreased progression of retinal nonperfusion in the second year, although only a subset of the patients were able to complete the clinical trial. Furthermore, progression of clinical disease and brain lesions was observed, which was a primary end point of the study.

Ruxolitinib, a Janus kinase (JAK) inhibitor has also shown promise in isolated cases with stabilization of RVCLS activity [4,14], with normalization of initially elevated CXCL10 mRNA in peripheral blood monocular cells (PBMCs) and a reduction of antinuclear autoantibodies. It has therefore been suggested that findings suggest that JAK inhibition may slow disease progression. However, we have attempted to treat numerous patients with RVCL using JAK inhibitors (Miner and group) and not observed promising results over the longer term. Given the fact that RVCL-S can sometimes exhibit a fluctuating disease course, as well as the fact that type I IFN levels are not typically elevated in RVCL[15], blockade of cytokine signaling might not be a preferred therapeutic option. Furthermore, a temporary delay in disease progression should be interpreted with caution, as this can occur naturally in patients with RVCL, and eventually disease progression resumes even in the face of immunomodulatory therapies.

Chauvin et al [16] have described human TREX 1 mosaicism causing retina limited RVCL with normal life span and have proposed gene therapy to synthetically create TREX 1 mosaicism as a potential treatment for RVCL. Their TREX 1 CRISPR/Cas9 prime gene editor therapy corrects the most common RVCL causing TREX 1 variant in cell culture and mouse models.

Occlusive telangiectasia have been associated with TREX 1 variants, as seen in Figure 6B. Patients diagnosed the cerebro-retinal vasculopathy type of this entity (Gass-Blodi type 3 macular telangiectasia), should undergo comprehensive systemic and genetic evaluation, to optimize management[17]. Ferrari et al [5] proposed diagnostic criteria for clinical recognition based on 78 patients from 11 unrelated families in different countries facilitating earlier recognition of RVCL-S.

Despite advances in understanding disease mechanisms and emerging therapies, there is no FDA approved treatment, and patients remain at high risk for premature death within 5-20 years after symptom onset.

Conclusion

We report a novel TREX1 frameshift variant, *c.802del p. (Arg268Glyfs*9)*, in a patient with RVCL-S, expanding the mutational spectrum of this rare disease and highlighting the importance of genetic testing in patients with retinal vasculopathy and cerebral white matter disease to facilitate early diagnosis, prevent unnecessary invasive procedures, and guide multidisciplinary management. The associated coagulation abnormalities suggest that patients, particularly those with thrombotic or atypical features, may benefit from antiphospholipid antibody screening, with potential implications for anticoagulation management despite limited guidelines. Further studies are needed to determine whether coagulative abnormalities represent a consistent feature of RVCL-S.

Declarations

Ethics approval: Formal Institutional Review Board (IRB) approval was not needed for this case report and signed written consent was obtained from the patient’s legal guardian for publication.

Patient consent:

Consent to publish the case report was obtained from patient's legal guardian (mother) as patient has developed dementia with memory issues. We obtained written informed consent to publish clinical details and Retina/ Neuroimaging without identifying details of the patient.

Competing interests:

The following authors have no financial disclosures: SC, ML, PCH, JJM, BL

Availability of data and materials: All clinical data supporting this case report is included within the published article.

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Author's contributions: SC analyzed and interpreted the patient data regarding the disease, conceptualized and was a major contributor in writing the manuscript. HPC performed the histological examination of the samples. ML and BLL were involved in critical review of the manuscript, editing, finalizing and providing references. JJM was involved with editing. All authors read and approved of the final manuscript.

Authorship: all authors attest that they meet the current ICMJE criteria for authorship.

Generative artificial intelligence was not used in writing this manuscript. The authors take full responsibility for the contents of this article.

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Figures

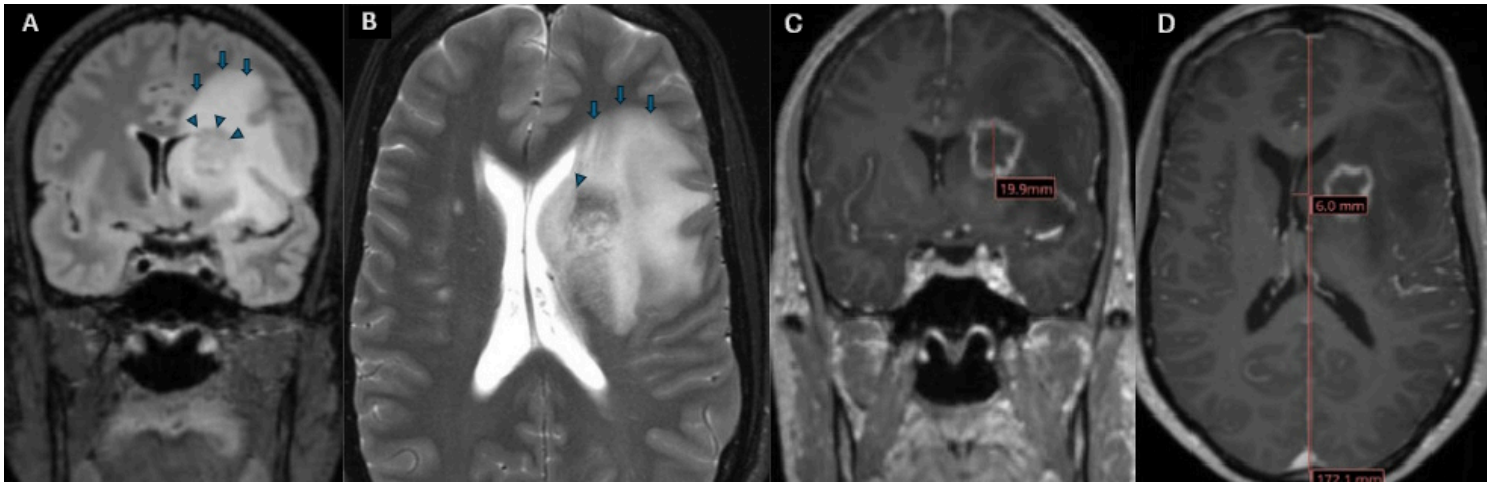


Figure 1

(A, B, C and D):

MRI brain with contrast T2 coronal and axial views show hyperintense left frontotemporal lesion with central necrotic center (A and B). T1 coronal and axial fat saturated views note hypointensity with ring enhancement of the lesions with gadolinium (C and D).

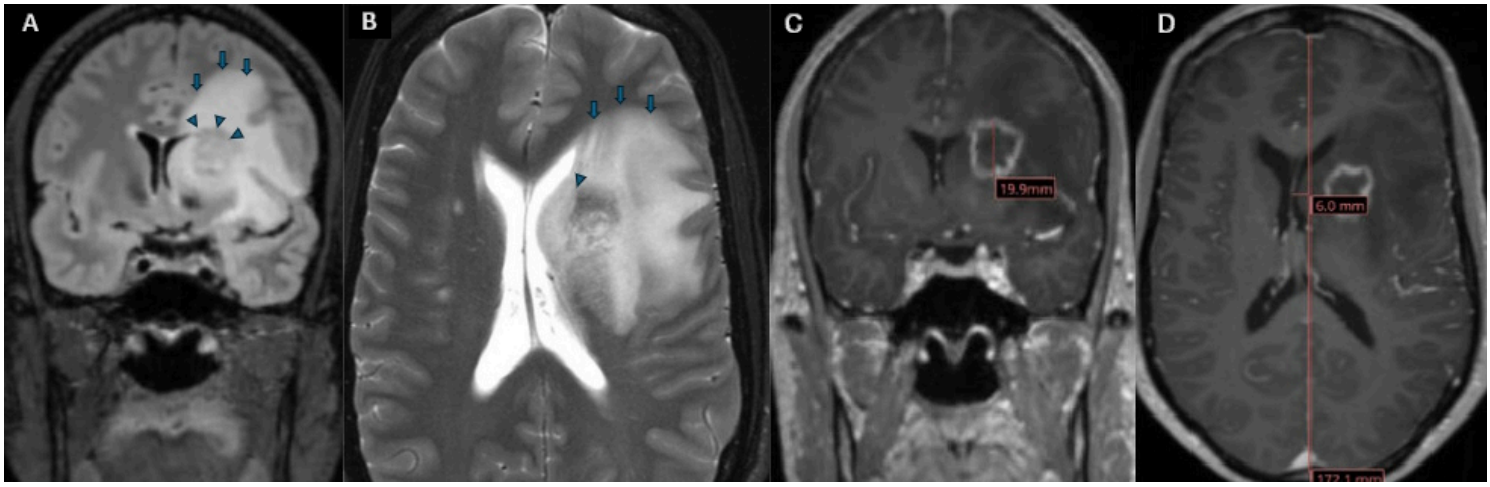


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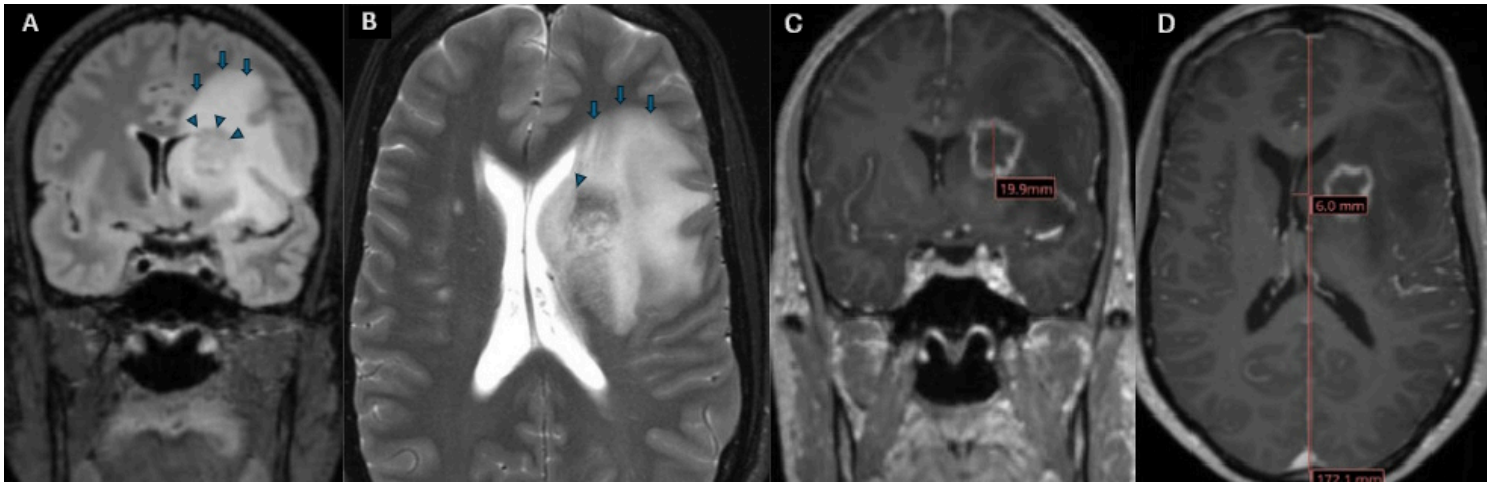


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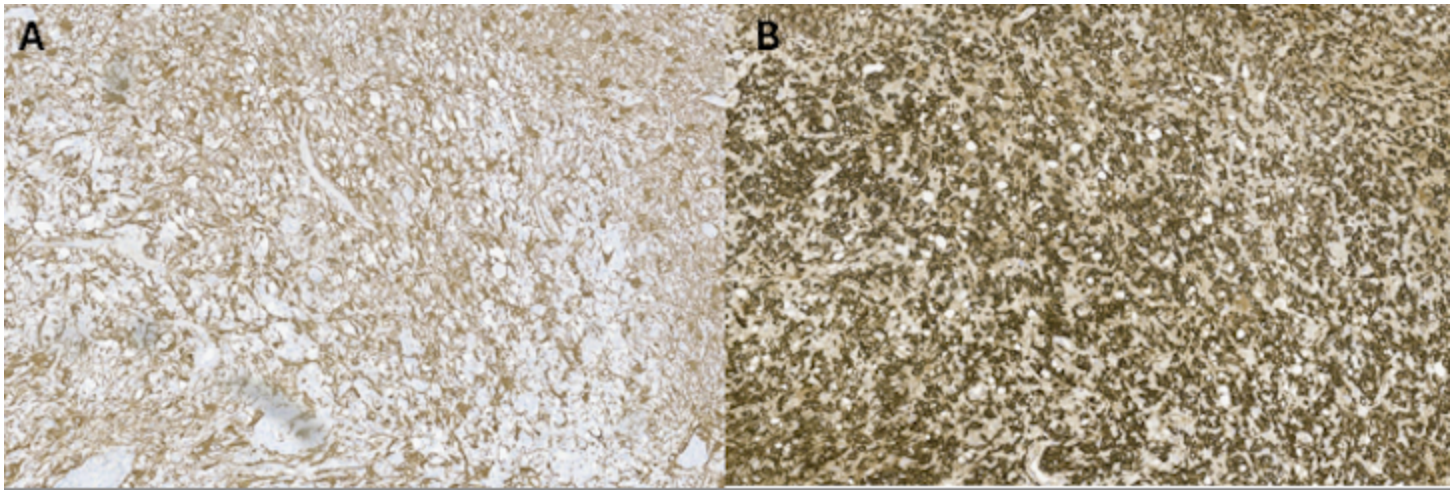


Figure 2

A: GFAP stain of the specimen shows reactive astrocytosis. Figure 2 B: CD163 highlights macrophage predominant response.

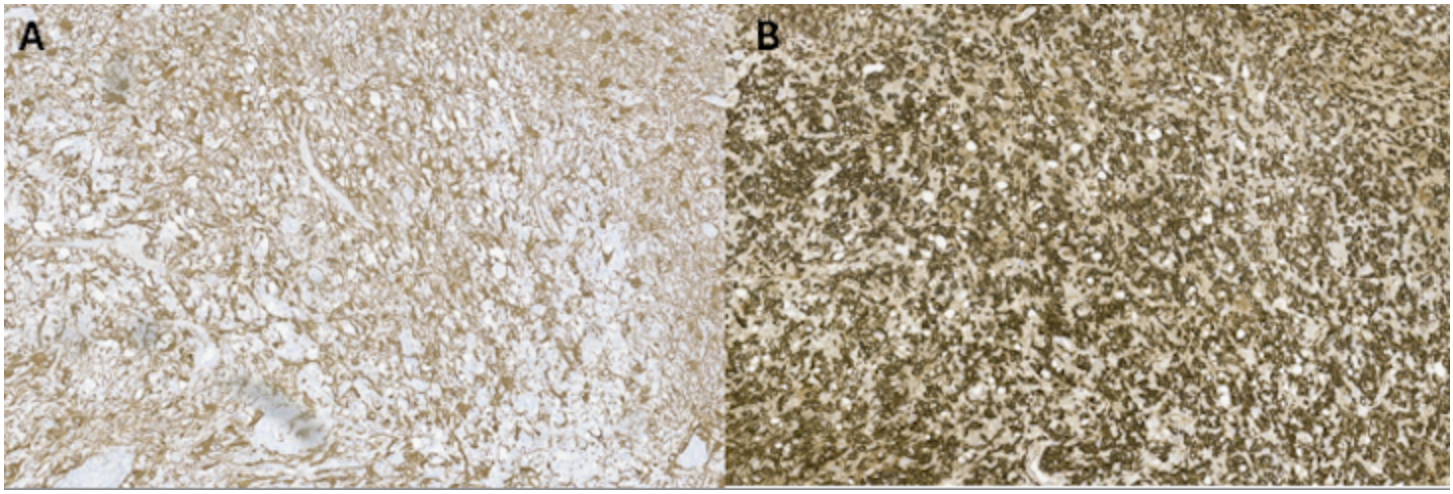


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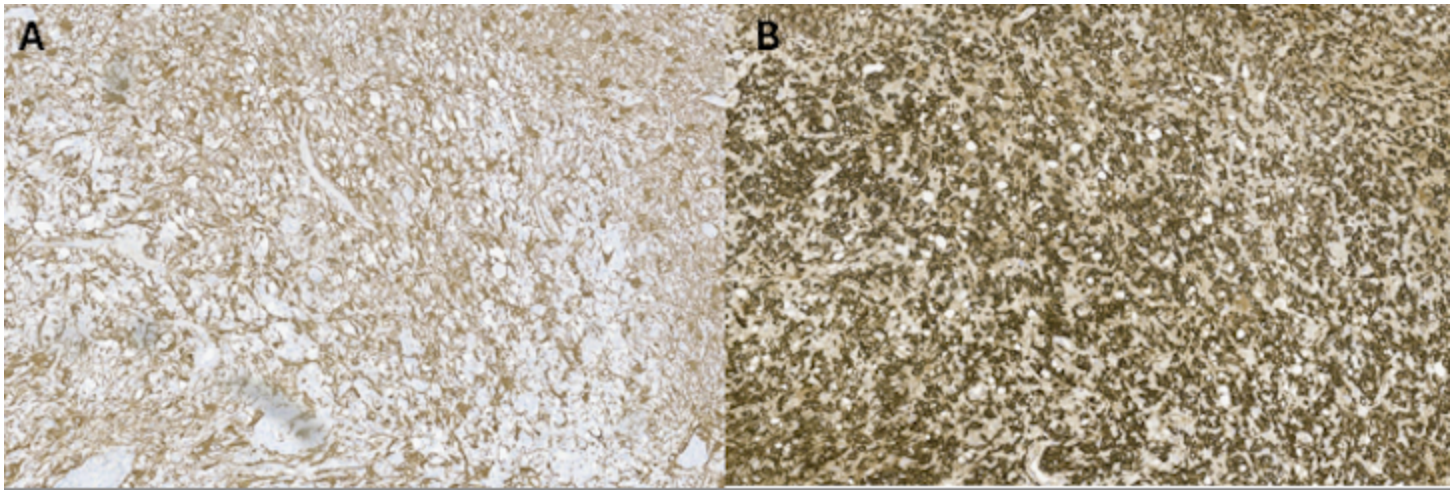


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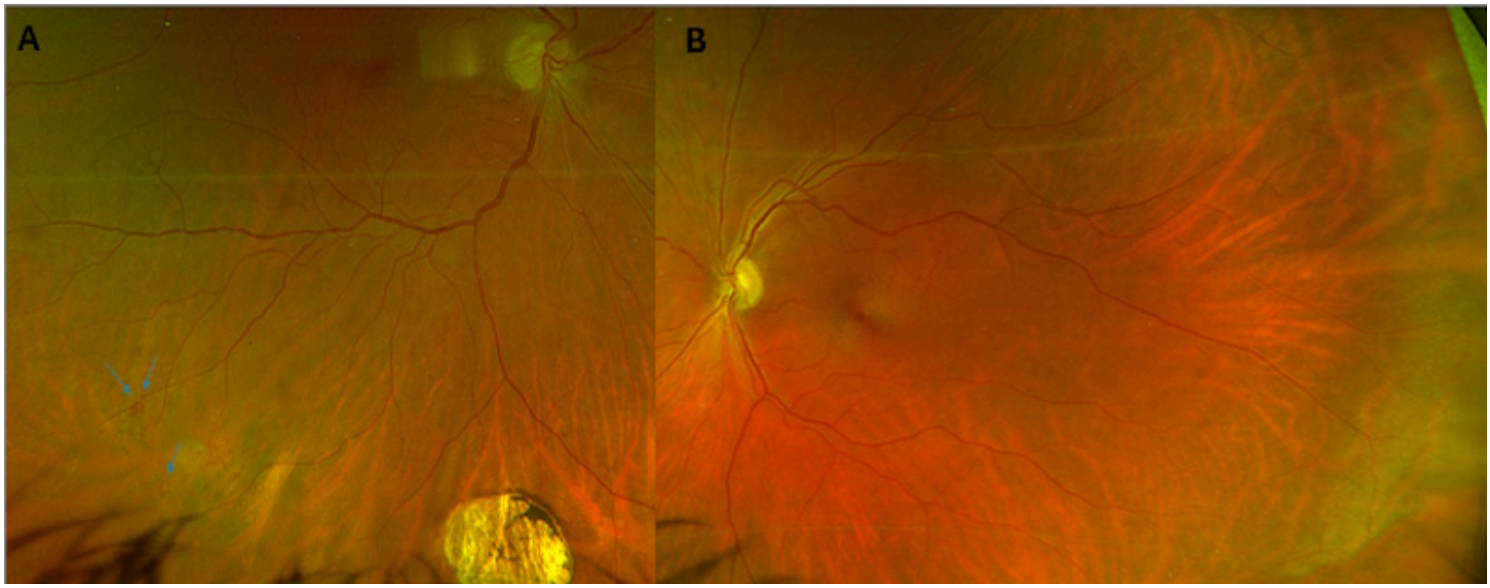


Figure 3

Optos fundus photos. A: Right eye shows temporal optic nerve pallor, peripheral neovascular tuft of vessels and retinopathy (blue arrows). B: Left eye shows temporal optic nerve pallor, peripheral avascular retina and retinopathy.

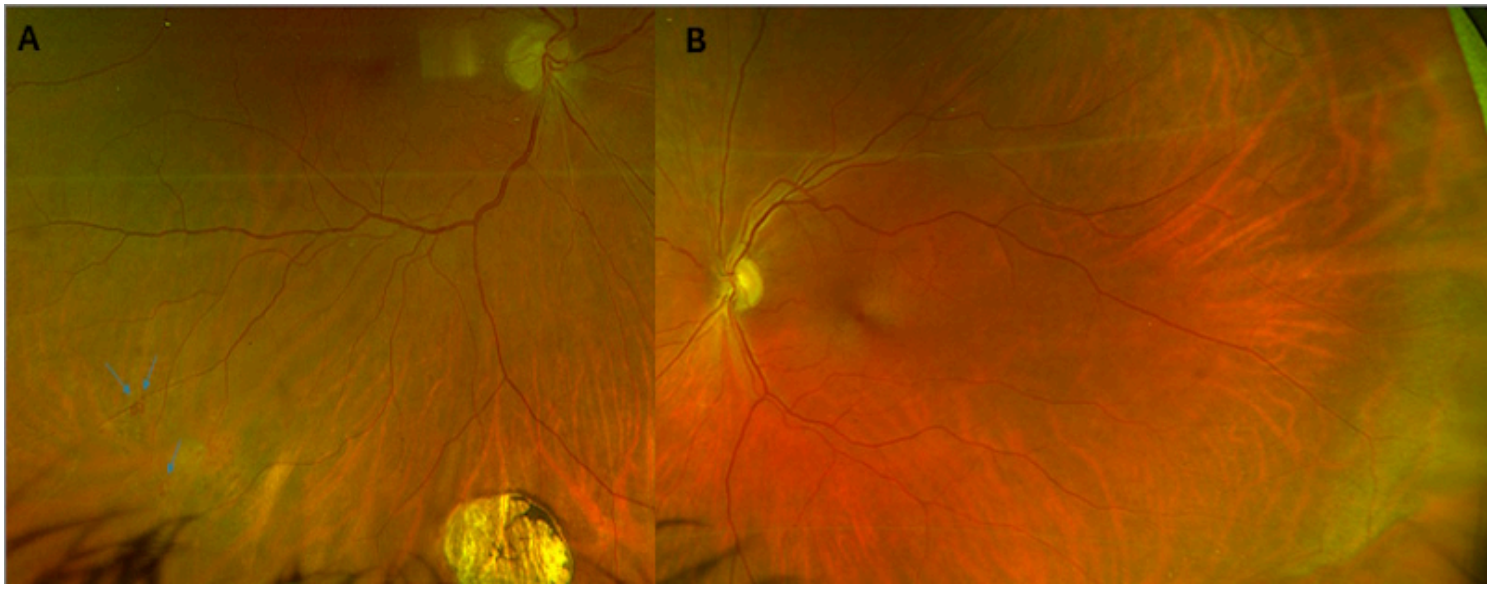


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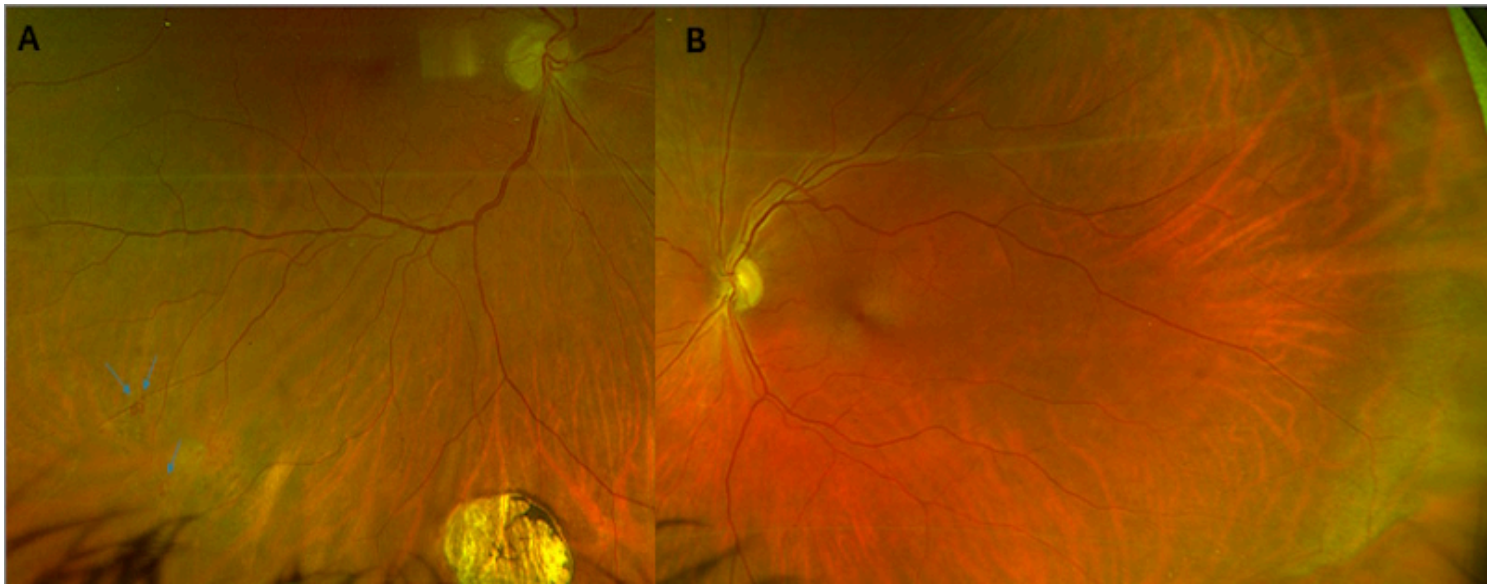


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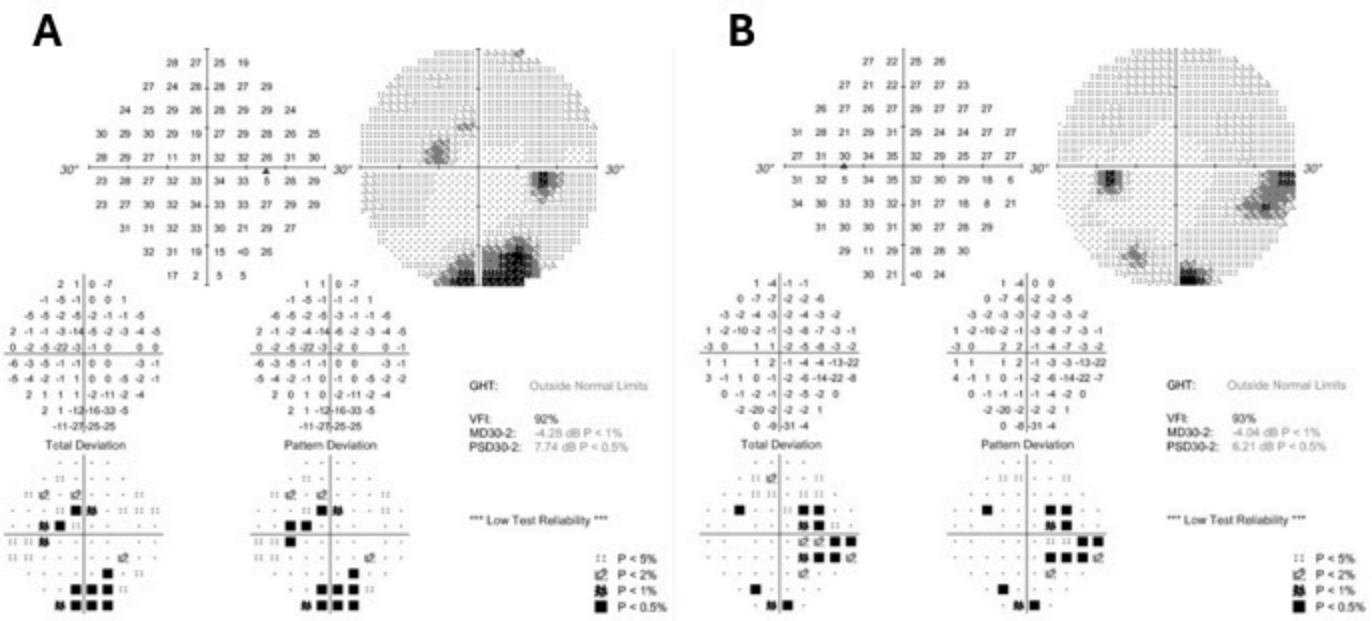


Figure 4

A: Humphrey visual field of right eye shows inferior and inferior nasal defects.

Figure 4 B: Humphrey visual field 30-2 of the left eye shows paracentral and inferior defects.

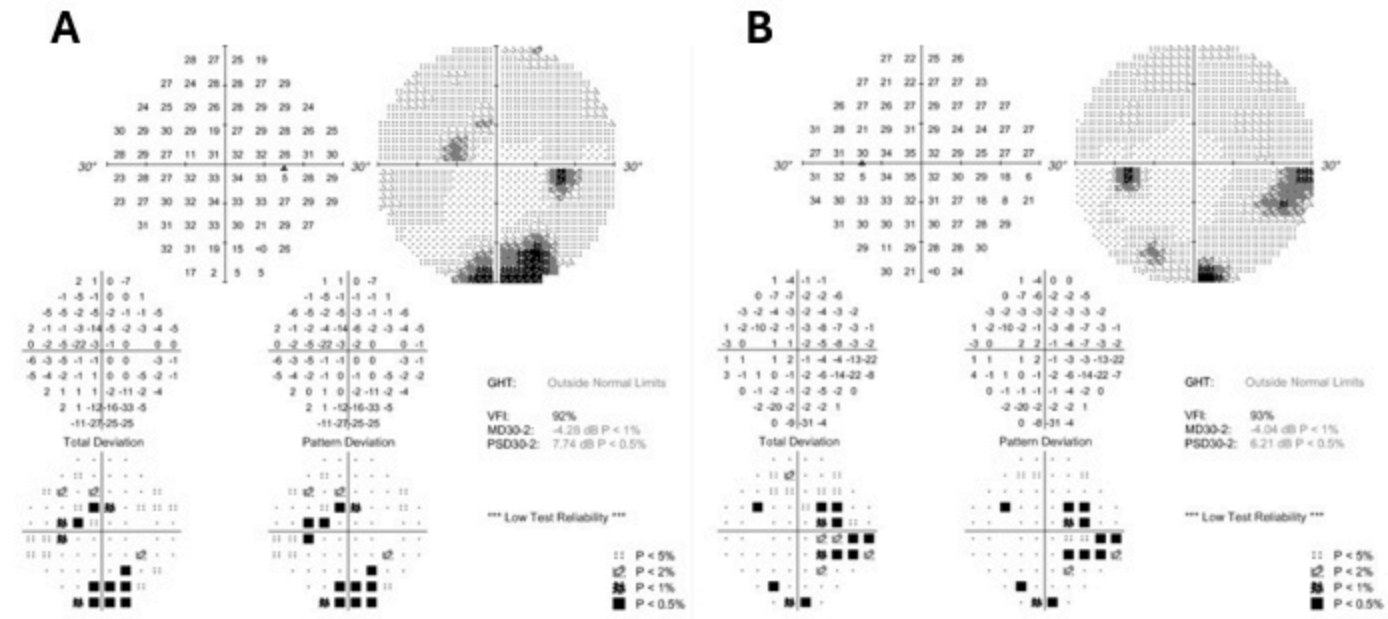


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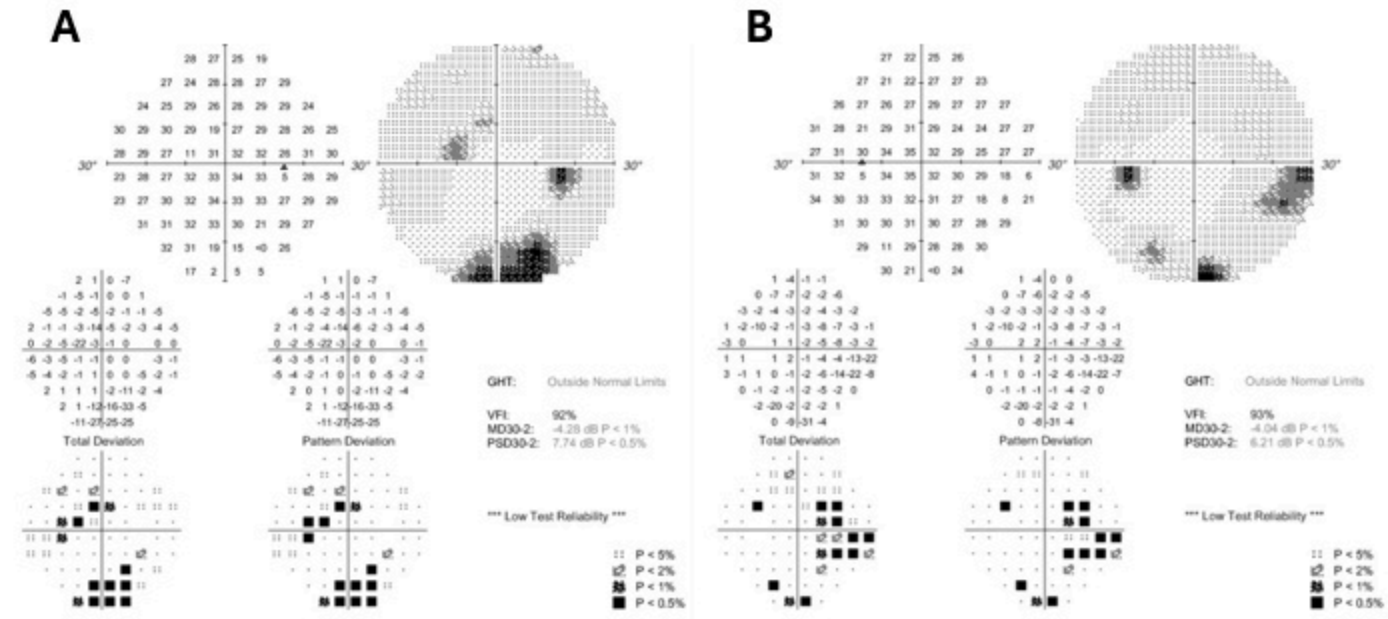


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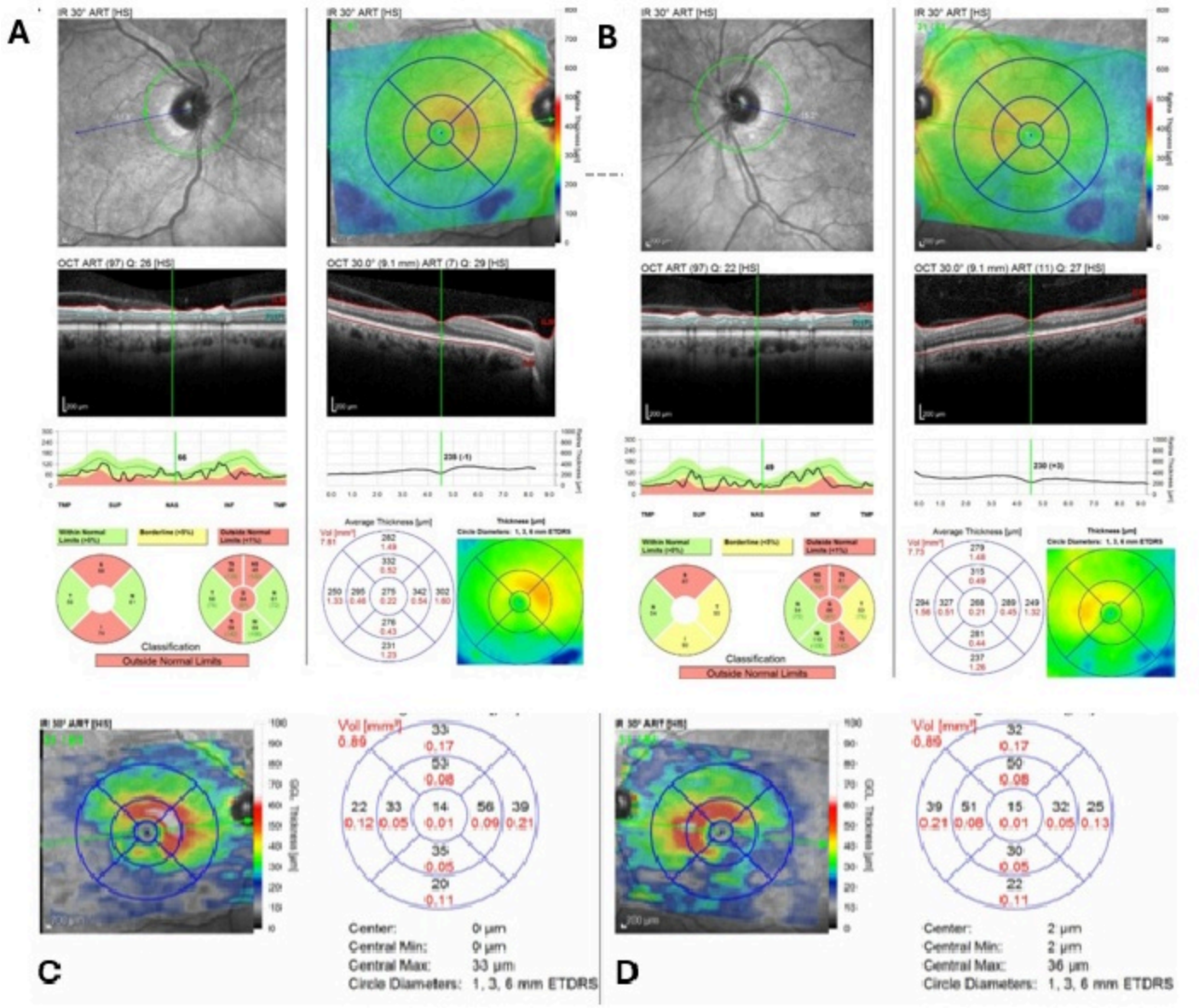


Figure 5

A: OCT of retinal nerve fiber layer in right eye notes thinning. Figure 5 B: OCT of retinal nerve fiber layer in left eye notes thinning. Figure 5 C: OCT of ganglion cell notes temporal wedge defect in right eye. Figure 5 D: OCT of ganglion cell notes temporal wedge defect in left eye.

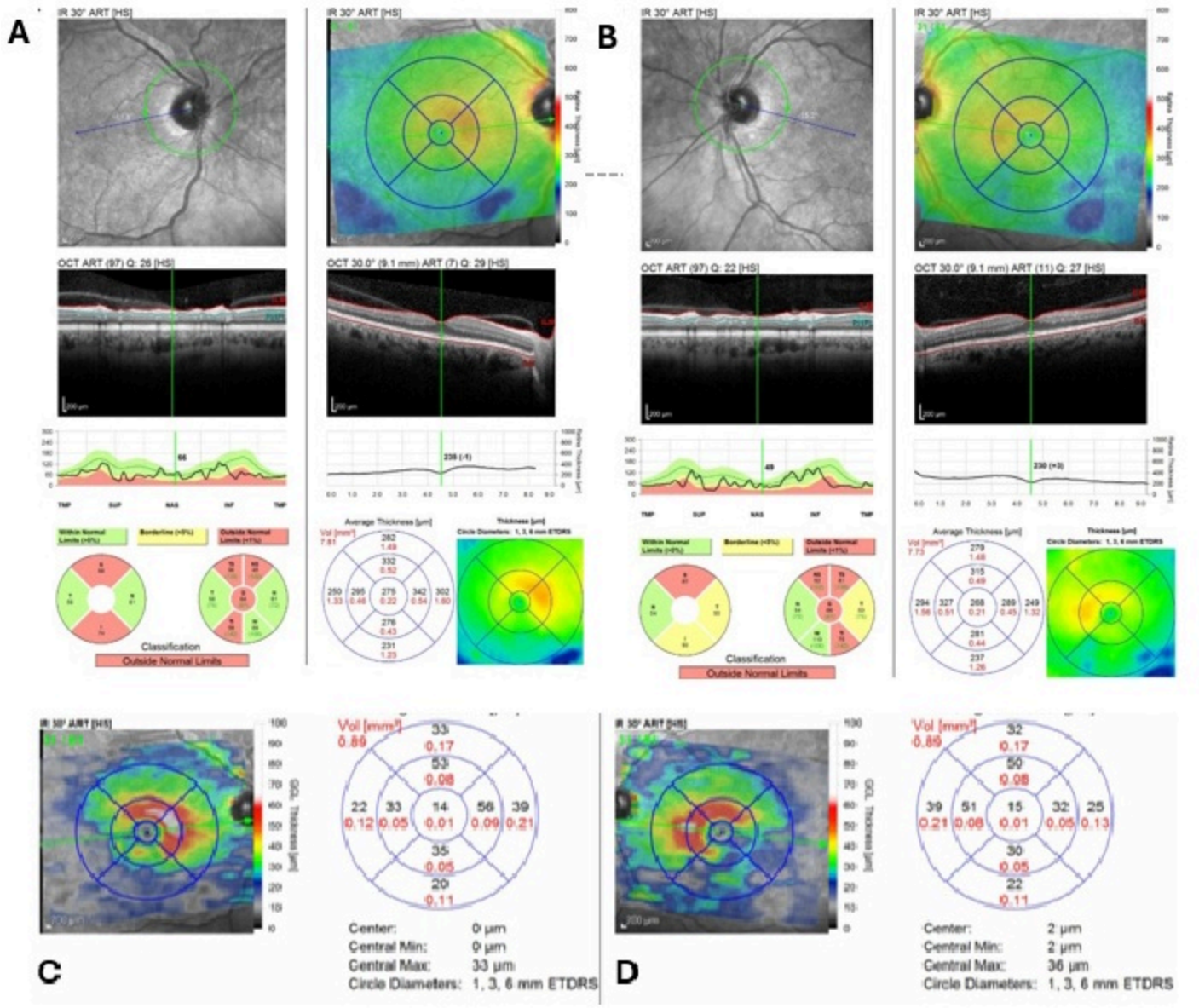


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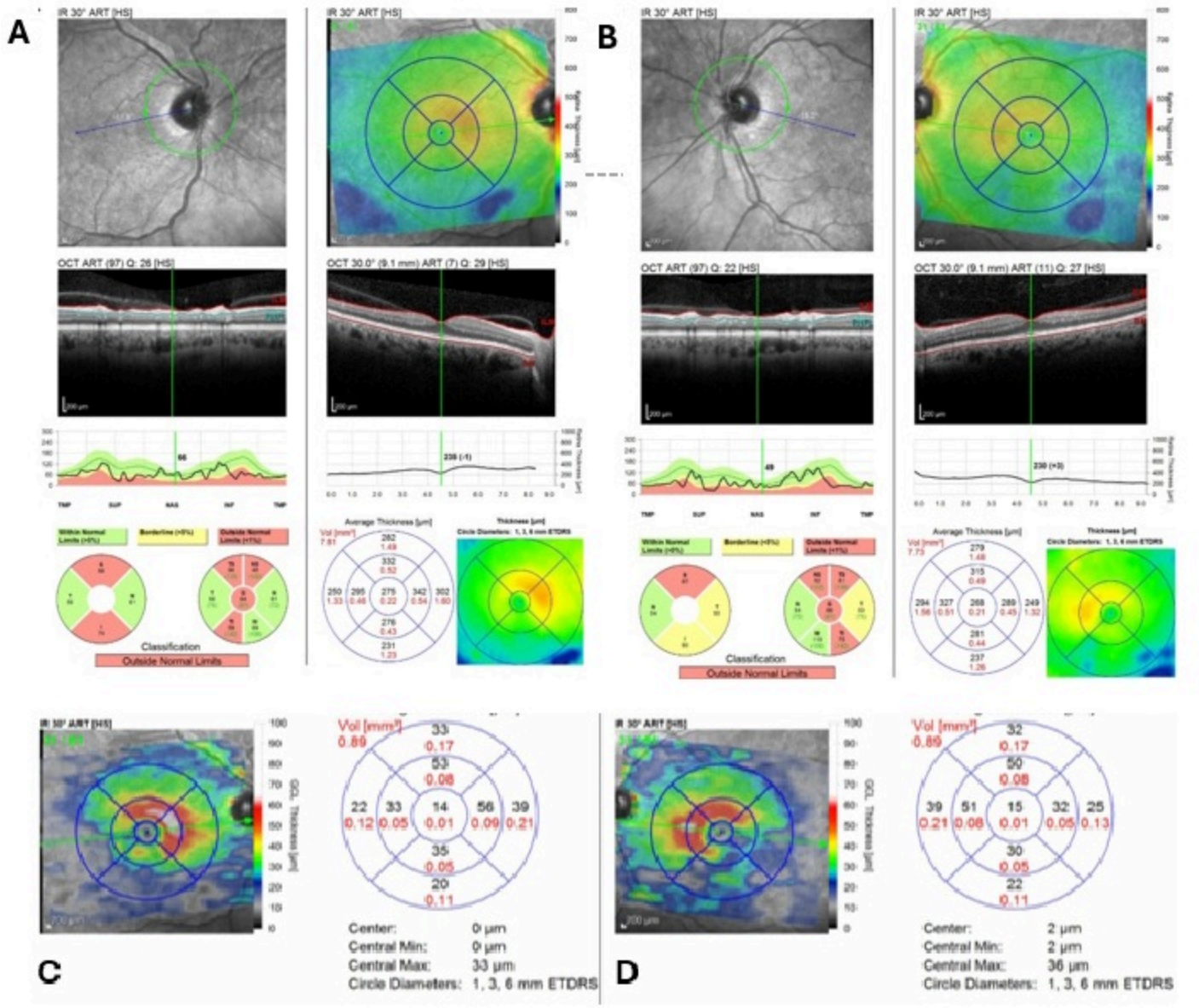


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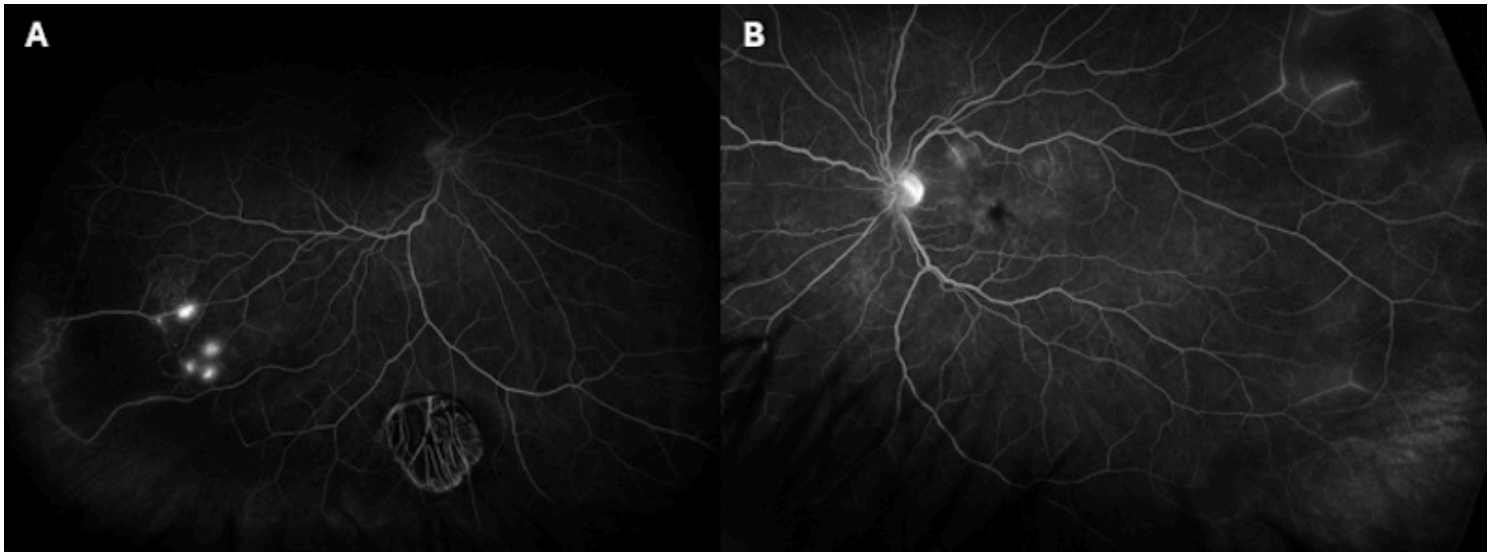


Figure 6

A: Late-stage fluoresceinangiogram shows areas of avascular periphery OD with neo-vascularization. Figure 6 B: Late-stage fluorescein angiogram OS showing a distorted foveal avascular zone with parafoveal leakage, peripheral occlusive vasculopathy and staining of the optic disc.

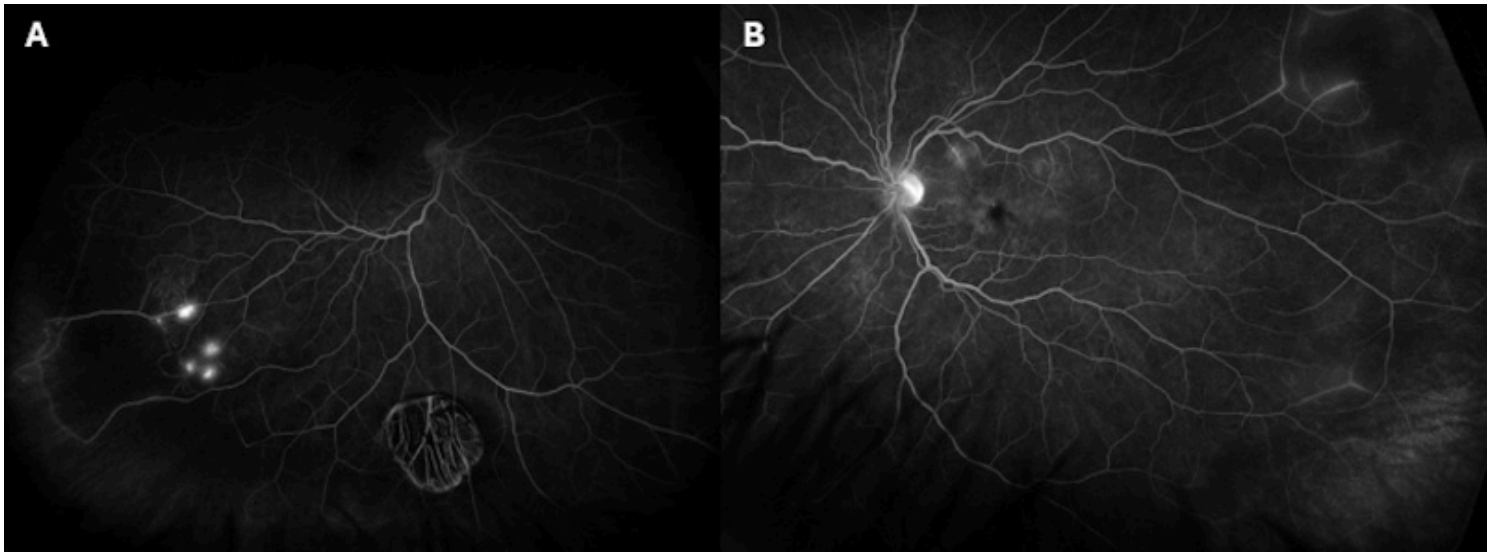


Figure 6

A: Late-stage fluoresceinangiogram shows areas of avascular periphery OD with neo-vascularization. Figure 6 B: Late-stage fluorescein angiogram OS showing a distorted foveal avascular zone with parafoveal leakage, peripheral occlusive vasculopathy and staining of the optic disc.

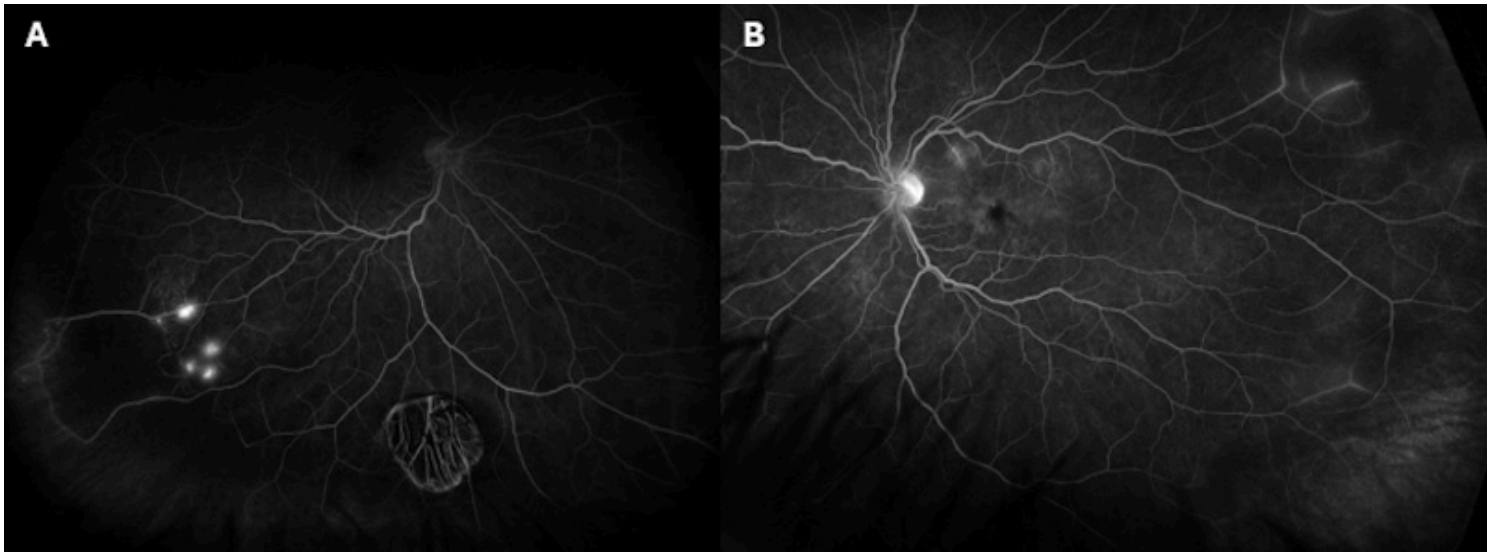


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