

Unilateral Acute Retinal Necrosis with Contralateral Optic Neuropathy as Initial Manifestations

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Case Report

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Abstract

Purpose: To report two rare cases of acute retinal necrosis (ARN) concurrent with contralateral optic neuropathy as the initial manifestation.

Methods: Observational case reports.

Results: Two cases of ipsilateral ARN accompanied by optic neuropathy in the contralateral eye are described.

A 71-year-old male presented with a painful right eye and light perception (LP) visual acuity (VA). Fundusoscopic examination revealed peripheral yellowish necrosis as well as perivascular hemorrhage in the right eye, with optic disc edema and wedged peripapillary hemorrhages in the contralateral eye. Best corrected visual acuity (BCVA) was 0.1 in the left eye. Despite systemic antiviral therapy and intravitreal injection (IVI) of Ganciclovir were administered, progression of optic atrophy in the left eye remained rapid, with VA preserved to LP. The second patient was a 54-year-old male with a 360° peripheral extension of necrotizing retinitis with hemorrhagic vasculitis in the right eye. Concurrent optic disc edema and peripapillary hemorrhages were observed in the left eye on initial presentation.

Conclusions and Importance: Our cases suggest that ARN can lead to ipsilateral necrotic lesions and concurrent optic neuropathy in the contralateral eye. Direct viral invasion can cause occlusion and dysfunction of the posterior ciliary arteries and choroidal vessels. Early recognition and prompt treatment of the contralateral eye may help avert severe visual loss.

Introduction

Acute retinal necrosis (ARN) represents a rare but vision-threatening uveitic syndrome characterized by severe necrotizing retinitis, occlusive vasculitis, and prominent vitreous inflammation [1, 2]. The condition is primarily attributed to reactivation of neurotropic herpesviruses, most commonly varicella-zoster virus (VZV) and herpes simplex virus (HSV) types 1 and 2 [3]. While the classic unilateral presentation with peripheral whitish retinal necrotic lesions is well-recognized, a defining and challenging feature of ARN is its significant potential for bilateral progression [4]. Notably, the contralateral eye may become involved in a substantial proportion of cases, sometimes after a latency period ranging from weeks to several years following the initial onset [5]. Herein, we report two rare cases of ARN presenting with contralateral optic neuropathy at initial onset, a distinctive manifestation that further highlights the bilateral and neuropathic nature of this syndrome.

Case presentation

Case 1

A 71-year-old male was referred to our institution with a 10-day history of progressively worsening blurred vision and pain in his right eye. The patient's family and past medical histories were unremarkable, with no history of immunosuppressive treatment or disease. Upon initial examination at our institution, his visual acuity (VA) was light perception (LP) in the right eye and 0.1 in the left eye. Slit lamp examination of the right eye revealed conjunctival chemosis and congestion, a few granulomatous keratic precipitates, and grade 2+ cells with 1+ flare in the anterior chamber. Ophthalmoscopic examinations displayed severe vitritis. The view of the posterior pole was poor, but peripheral confluent whitish lesions and perivascular hemorrhage was barely visible in the right eye (Fig. 1A). There were no necrotic lesions or retinitis in his left eye, but the margin of the optic disc was mildly blurred (Fig. 1B). Same-day laboratory investigations revealed normal full blood count and liver/kidney function tests; serology for *Treponema Pallidum* and HIV was negative.

Fluorescein angiography (FA) demonstrated optic disc hyper-fluorescence, along with vasculitis, arterial occlusion, and extensive retinal hypoperfusion in the right eye (Fig. 1C). Of note, blurred optic disc margins with mid-to-late phase leakage, and the filling of both choroidal and retinal arteries were delayed in the left eye. (Fig. 1D).

A presumptive diagnosis of ARN in the right eye was made, and systemic acyclovir treatment (2400 mg/d, intravenously) was started and oral prednisone (45 mg/day) was administered 24 hours later. Tropical levofloxacin was administered for prophylactic secondary infection. One day after hospitalization, the vitritis in the right eye progressed significantly. The patient was treated with one dose of intravitreal injection (IVI) of ganciclovir (2mg/0.1ml). Metagenomic sequencing was performed on aqueous humor obtained via anterior chamber paracentesis returned positive for VZV. Two days later, he accepted prophylactic pars plana vitrectomy (PPV) and silicone oil (SO) tamponade for the right eye due to aggravation of vitreous inflammation and progression of necrotic foci. Postoperatively, the retinitis was quiescent and the patient continued to receive oral valacyclovir 1000mg three times a day.

When the patient revisited our hospital 13 days after the onset of the ARN in the right eye, he complained of progressively vision loss in his left eye and BCVA was 0.06. Funduscopy examination of the left eye revealed necrotic lesion in the peripheral naso-superior quadrant and optic disc edema (Fig. 1E). The patient underwent intravitreal ganciclovir (2mg/ 0.1ml) treatment in his left eye and continued oral valacyclovir therapy. The metagenomic sequencing for aqueous humor of left eye revealed positive for VZV and Epstein Barr virus (EBV). He was received the second dose of intravitreal ganciclovir three days afterward. During the period from 5th to 10th day postoperatively, the necrotic foci in the left eye showed limited progression, but the optic disc gradually transitioned from edema to pallor (Fig. 1F and 1G). The spectral domain-optic coherence tomography (SD-OCT) demonstrated the thickness of retinal neuronal fiber layer in the left eye was significantly decreased. Despite no progression of necrotic lesion was observed in the left eye, however, the patient's vision persists at low level with questionable LP in the right eye and LP in the left eye.

Case 2

A 54-year-old male referred to our institution with blurred vision and conjunctival congestion in his right eye. The BCVA of the right eye was 0.25 and 1.0 in the left eye. Slit-lamp examination demonstrate keratic precipitates, anterior chamber cells in his right eye. Fundoscopic examination revealed vitreous haze and coexistence of peripheral retinal necrosis and hemorrhagic vasculitis (Fig. 2A). Notably, significant optic disc swelling and splinter parapapillary hemorrhages were observed in his left eye (Fig. 2B). FA demonstrated filling delays in both the arterial and venous phases with occlusion of the peripheral retinal vessels in the right eye; and optic disc hyper-fluorescence and parapapillary vascular leakage with no peripheral ischemia or leakage in the left eye (Fig. 2C and 2D).

The patient was diagnosed with ARN and treated with intravenous acyclovir 800mg three times per day and 60mg prednisone. He was also received intravitreal ganciclovir (2mg/0.1ml) in the right eye. After two days of treatment, the grayish-white necrotic area of the right eye continued to expand, circumferentially fuse, and progressively extend toward the posterior pole. He then underwent PPV and SO tamponade to prevent retinal detachment. Metagenomic sequencing on the vitreous sample confirmed VZV was positive. Two days after surgery, fundus examination revealed the necrotic lesion of the right eye was in a static state (Fig. 3A). Notably, scattered yellowish lesions were observed in the inferior and inferotemporal quadrants of the left eye (Fig. 3B). He was then started with intravitreal ganciclovir treatment in the left eye. With continued systemic antiviral therapy and a second intravitreal dose of ganciclovir, the necrotic lesion was contained, but the optic disc remained edema and migratory peripapillary hemorrhage was persisted in his left eye (Fig. 3C). Besides, SD-OCT demonstrated macular edema, and parafoveal hemorrhage was also noted in the left eye (Fig. 3D). From postoperative day 10 to day 20, retinal inflammation showed no signs of activity bilaterally, and macular edema gradually receded. Accordingly, oral prednisolone was tapered off. The temporal side of the optic disc in the left eye appeared pale, with no evident enlargement of the optic cup (Fig. 3E). BCVA in the right eye was 0.03 and 0.12 in the left eye.

Discussion

Acute retinal necrosis syndrome is characterized by progressive necrotic retinal lesions and vasculitis, predominantly involving the arteries [6]. It is intuitive that the resulting obliterative arteritis causes secondary ischemic injury to both the retina and the optic nerve (ON), which leads to intraneural inflammation and ischemic necrosis ensues [7].

Optic neuropathy preceding ARN has been reported not only in immunocompromised patients, specifically those with AIDS, but also in immunocompetent individuals [8, 9]. Notably, ON impairment in those cases was largely confined to the ipsilateral ARN eye. In contrast, the two cases in this series are unique in demonstrating one eye with typical retinal necrosis and concurrent optic neuropathy as an initial presentation in the contralateral eye. Diagnosis of this condition was difficult until the classic presentation of peripheral necrosis developed. Despite adequate antiviral therapy, progression of ON damage persists, in contrast to the comparatively indolent course of retinal lesions. FA results of the case 1 revealed markedly filling defect in both the choroidal and retinal vascular systems, suggesting the

possibility of hypoperfusion of the dual vascular system. This raises the question of whether the contralateral optic impairment represents arteritic anterior ischemic optic neuropathy (AAION) secondary to viral infection [8, 10]. However, what remains unexplained by the current evidence is why does occlusion or hypoperfusion occurred in these vessels—which have larger luminal diameters and greater blood flow—rather than in the retinal vascular system, in the initially non-necrotic eye? Given the unavailability of biopsy, the precise mechanism of the vascular permeability remains speculative.

The potential cause for progressive optic pallor developed alongside a poor VA prognosis in the left eye of case 1 may lies in the co-infection of VZV and EBV. Since viral co-infection has been documented to result in both orbital and intraocular inflammation [11], conventional acyclovir dosing or monotherapy may be insufficient in effectively suppressing this type of pathological process [12]. Comparatively, although the optic disc swelling and parapapillary hemorrhage was also observed in the non-necrotic eye of the case 2, visual function was partially preserved and remained above critically deficient levels. One plausible explanation is that the optic neuropathy was secondary to hypoperfusion of the posterior ciliary arteries, while the retinal vascular system was relatively spared. Furthermore, the development of optic disc pallor in the late stage serves as corroborative evidence for a shared pathogenesis with the AION in the left eye.

Emerging evidence underscores interleukin-6 (IL-6) as a pivotal orchestrator of inflammatory and neurodegenerative pathology, with parallel roles observed in the context of ARN and CNS inflammation [13, 14]. Elevated IL-6 levels in the aqueous humor have been documented not only as a biomarker of inflammation but also as a significant correlate of disease severity and complications, including retinal detachment [13]. This suggests that IL-6-driven inflammation is a critical contributor to the rapid retinal tissue destruction and blood-retinal barrier compromise [15]. Based on the cytokine analysis of aqueous humor of the contralateral eyes collected during the IVI, we found significantly elevated levels of IL-6 and decreased levels of vascular cell adherence molecule-1 (VCAM-1) in this case series compared to five patients with ipsilateral ARN lesions that spared the contralateral eye (data not show). These observations suggest that elevated IL-6 and reduced VCAM-1 levels may serve as potential biomarkers for monitoring the progression of contralateral ARN induced optic neuropathy. Therefore, future studies on the crosstalk of IL-6 and VCAM-1 are warranted, and IL-6/IL-6R blockade may offer a promising therapeutic strategy to mitigate bilateral ARN progression and associated ON injury.

In conclusion, we report rare cases of ipsilateral ARN with concomitant optic neuropathy in the contralateral eye, highlighting the ON impairment can be an initial and independent damage units other than retinal necrosis. Our findings underscore the importance of early recognition of this disease entity to guide individualized management, and suggest that prompt aggressive antiviral therapy may yield prognostic benefits.

Declarations

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Authors' contributions

YPL: Investigation, Writing- Original draft preparation. WC: collected, analyzed and interpreted the data. XZ: provide data. XW: Supervision. YQL: Collect and organize data. FYZ: did review. ZZ: Project administration, Writing- Reviewing and Editing, Funding acquisition.

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Availability of data and materials

The datasets generated and analysed during the current study are available in the BioProject repository (National Genomics Data Center, NGDC), accession number subPRO105512, available at <https://ngdc.cncb.ac.cn/gsub/submit/bioproject/subPRO105512>.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University. All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Consent for publication

Written informed consent for the publication of clinical details and identifying images was obtained from all participants enrolled in this study.

Competing interests

The authors declare no competing interests.

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Figures

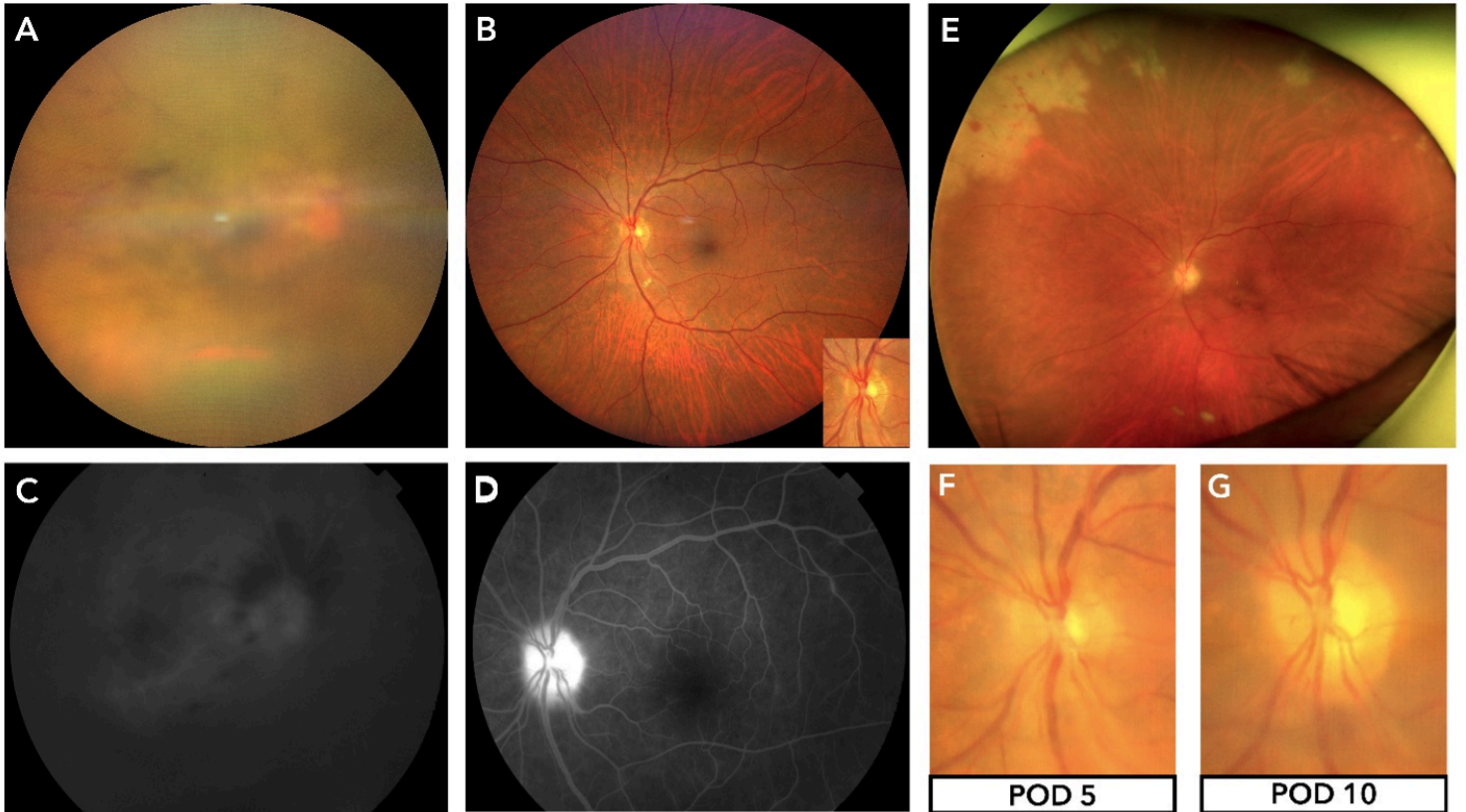


Figure 1

Images of Case 1, Fundus photograph and fluorescein angiography (FA) at initial presentation. A. Fundus image of the right eye showing severe vitreous opacities and circumferential retinal necrosis. B. Fundus image showing a blurred optic disc margin without evident retinal necrotic lesions in the left eye. Higher-magnification view demonstrating the morphology of the optic disc C. fluorescence images showing filling defects in both the choroid and retinal vasculature of the right eye. D. Delayed filling and optic disc hyperfluorescence in the left eye In the early arterial phase of angiography. E. fundus photograph revealing necrotic lesion in the peripheral naso-superior quadrant in the left eye. F and G. Images showing the course of optic disc edema in the period of post-operative day (POD) 5 and 10.

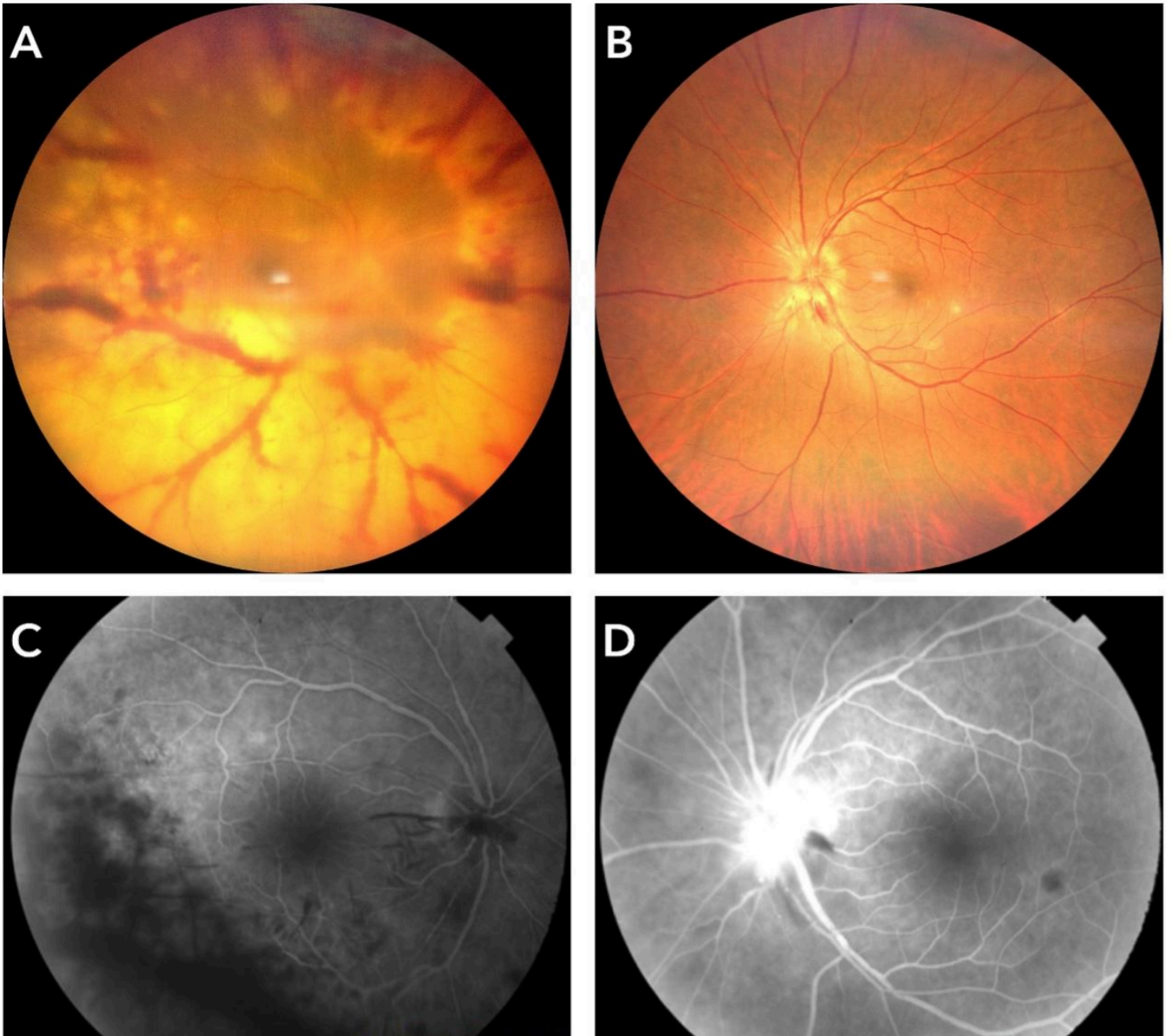


Figure 2

Images of Case 2, baseline images of fundus photograph and fluorescein angiography. A. The fundus images of the right eye showing the vitreous opacities, circumferentially extensive necrotic lesions and peri-vascular hemorrhages. B. Optic disc swelling and parapatillary hemorrhages were observed in the left eye. C. fluorescence images showing filling defects and fluorescence blockage of the right eye. D. Delayed filling and optic disc hyperfluorescence in the left eye In the early arterial phase of angiography.

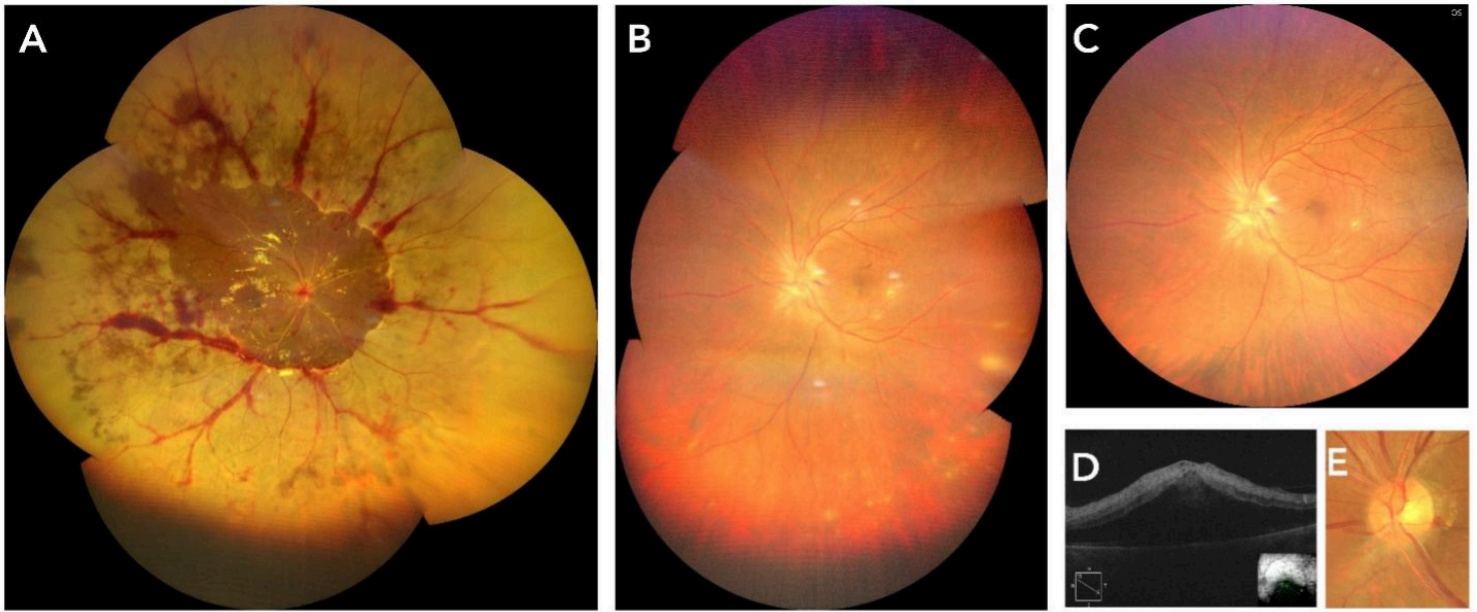


Figure 3

Images of Case 2, A. Fundus image of the right eye showing confluent circumferential retinal necrosis (post-vitrectomy with oil tamponade). B. Scattered necrotic lesions in the peripheral temporal and inferior quadrants of the left eye. C. Images showing persisted optic disc edema and migratory peripapillary hemorrhage in the left eye. D. Optical coherence tomography (OCT) showing macular edema in the left eye. E. Temporal pallor of the optic disc in the left eye.