



Case report

Bilateral acute retinal necrosis caused by two separate viral etiologies

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ABSTRACT

Purpose: To describe an unusual case of bilateral acute retinal necrosis (ARN) that was caused by varicella zoster virus in one eye and Epstein-Barr virus in the fellow eye.

Observations: A 67-year-old immunocompromised man presented with ARN in the left eye following a dermatomal vesicular rash, with an aqueous sample positive for varicella zoster virus. Four months later, the patient presented with panuveitis and serous retinal detachment in the right eye, with vitreous sample positive for Epstein-Barr virus and negative for varicella zoster, herpes simplex, and cytomegalovirus.

Conclusions and importance: We report a rare case of bilateral ARN with independent infection of each eye by different viruses; varicella zoster in the left eye and, four months later, Epstein-Barr virus in the right eye. Immunocompromised patients are vulnerable to ARN from any of its inciting viral causes, and intraocular fluid should be obtained for diagnostic confirmation from the second eye in cases of bilateral ARN.

1. Introduction

Acute retinal necrosis (ARN) is an infectious retinitis and retinal vasculitis characterized by prominent vitreous inflammation and progressive retinal necrosis.^{1,2} Viruses implicated in causing ARN include varicella zoster (VZV), which accounts for most cases, as well as herpes simplex viruses (HSV) 1 and 2, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).³⁻⁵ Without antiviral treatment, involvement of the fellow eye occurs in about 70% of patients within weeks to years.⁶⁻⁸ Late complications can include retinal detachment and macular ischemia, and visual prognosis is generally guarded.⁹⁻¹¹

While bilateral ARN is well-reported in the literature,^{6,7} no case to our knowledge has demonstrated laboratory evidence of two separate viral etiologies in a patient with bilateral ARN. We present a case of bilateral ARN in an immunocompromised male who presented with acute retinal necrosis secondary to VZV in the left eye, then later developed signs of systemic EBV with EBV-positive and VZV-negative ARN in the right eye.

1.1. Case report

A 67-year-old man with history of lupus nephritis presented for retinal evaluation with a 7-day history of floaters and blurred vision in the left eye. His medications included hydroxychloroquine 200mg daily, mycophenolate mofetil (Cellcept) 1000 mg twice daily, and prednisone 10 mg daily. He had been hospitalized 1 month earlier for

treatment of community-acquired pneumonia, at which time he was also noted to have a dermatomal vesicular rash along his left groin. He was diagnosed with varicella zoster infection and treated with 7 days of intravenous acyclovir followed by a 3-day course of valacyclovir 1 g by mouth twice daily.

At presentation, his best-corrected visual acuity was 20/25 in the right eye and 20/100 in the left eye. Slit-lamp examination was normal in the right eye, and the left eye was notable for trace conjunctival injection and 2+ cell in the anterior chamber. Examination of the right fundus was normal. Fundus examination of the left eye revealed 1+ vitritis, few mid-peripheral intraretinal hemorrhages, and peripheral scalloped hypopigmented lesions with pigmented posterior borders in all quadrants of the peripheral retina (Fig. 1). An anterior chamber paracentesis of the left eye was performed, and the aqueous sample was positive for VZV by polymerase chain reaction (PCR) and negative for HSV and CMV. The patient was treated with valacyclovir 1 g three times per day and three intravitreal injections of foscarnet. Over the next several weeks, the vitritis improved, the retinal lesions healed with atrophic changes and mottled pigmentation, and visual acuity improved to 20/50. Six weeks later, the patient developed a retinal detachment in the left eye that was treated with pars plana vitrectomy, scleral buckle, laser, and silicone oil tamponade. The patient was maintained on valacyclovir 1 g three times per day postoperatively with sustained reattachment and quiescence (Fig. 2B).

Four months after initial presentation, the patient presented urgently for pain, redness, and vision loss in the right eye. The visual

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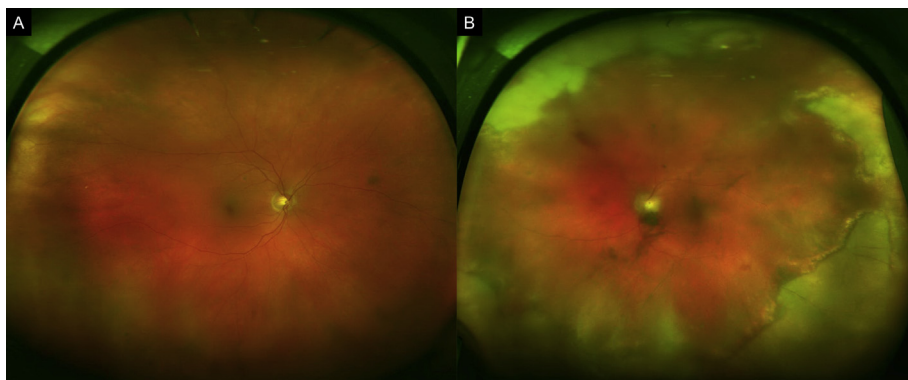


Fig. 1. Optos fundus photography of both eyes at presentation. **A** The right eye is normal. **B** The left eye is remarkable for 1+ vitreous haze, few mid-peripheral intraretinal hemorrhages, and scalloped necrotic lesions with pigmented posterior border in all quadrants of the peripheral retina. PCR of aqueous sample of the left eye was positive for varicella zoster virus and negative for cytomegalovirus and herpes simplex virus.

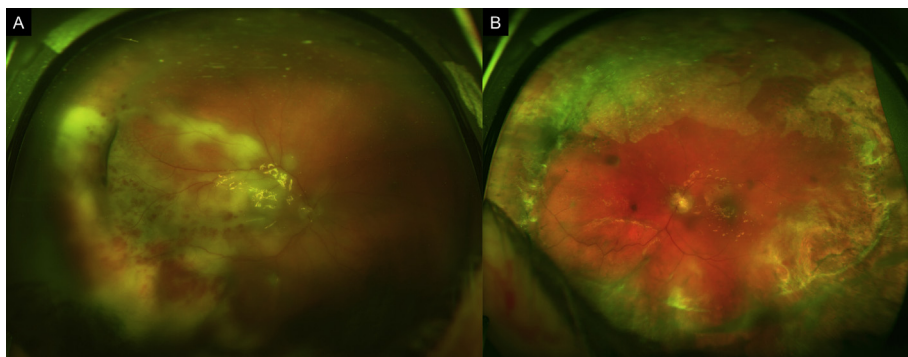


Fig. 2. Optos fundus photography of both eyes six months after initial presentation. Photographs demonstrate new onset of acute retinal necrosis due to Epstein-Barr virus (right eye) that began two months ago and healed varicella zoster virus lesions (left eye) that presented 6 months before the photographs were taken. **A** The right eye contains silicone oil and is notable for white areas of necrotizing retinitis associated with subretinal infiltrates temporally that extend into the macula. There is a scleral buckle effect with shallow retinal elevation in the infratemporal quadrant. The right eye vitreous sample was positive for Epstein-Barr virus and negative for varicella zoster virus and cytomegalovirus. **B** The left eye demonstrates retinal detachment with silicone oil and a scleral buckle effect in the periphery. In the periphery there are nearly confluent patches of atrophic retina with granular pigmentation.



Fig. 3. Photograph of the patient's protruded tongue reveals the characteristic appearance of oral hairy leukoplakia, including vertically corrugations and thick furrows within a white plaque. Oral hairy leukoplakia is a sign associated with active Epstein-Barr virus infection in the immunocompromised.

acuity in the right eye was hand motions, and slit lamp examination was notable for 3+ conjunctival injection, fine keratic precipitates, 2+ cell in the anterior chamber, and posterior synechiae. There was 2+ vitritis, and fundus exam was notable for a bullous temporal retinal detachment without breaks or tears. The patient was taken to the

operating room for repair of the retinal detachment the following day and underwent pars plana vitrectomy, lensectomy, scleral buckle placement, laser, and silicone oil fill. Intraoperatively, significant vitreous debris and abscesses were apparent. The retina appeared white, consistent with necrotizing retinitis. No breaks were identified, indicating that he had a serous retinal detachment. An anterior retinotomy was made superiorly and subretinal fluid was aspirated after perfluoro-N-octane (PFO) was injected. The subretinal fluid was proteinaceous and milky. The vitrectomy specimen was submitted for culture and molecular diagnostics, and the PCR was positive for EBV and negative for VZV, HSV, and CMV. Of note, during induction of anesthesia, the patient was noted to have a diffuse, white plaque over his tongue that was vertically corrugated and thickly furrowed (Fig. 3). An infectious disease consultation confirmed suspicion for oral hairy leukoplakia, a clinical sign associated with active EBV infection in immunocompromised patients. Postoperatively, the right eye demonstrated an area of retinal necrosis temporally with associated hemorrhage and a white, subretinal infiltrate. There was a scleral buckle effect with retinal elevation infratemporally and nasally. (Fig. 2A). One month later, the patient presented again with right eye pain and hand-motions acuity with an intraocular pressure of 46 mmHg. The increased intraocular pressure was associated with anterior chamber flattening from a worsening serous retinal detachment. He underwent cyclophotocoagulation of the right eye and remains comfortable with no light perception (NLP).

2. Discussion

Bilateral ARN usually occurs sequentially, with the second eye affected weeks to years after the first.⁷ While the mechanism of viral spread is not fully understood, viral propagation may occur through axons along the optic nerves and chiasm.¹² The timing of fellow eye involvement depends on virus latency and host immune response.

Treatment with systemic antivirals reduces rate of second-eye involvement, and immunocompromised individuals require longer duration of intravenous antiviral treatment for systemic VZV.⁴ Our case presents a unique presentation of bilateral ARN due to separate inciting viruses, with the first eye PCR-positive for VZV and the second eye PCR-positive for EBV and negative for VZV. Both eyes were negative for HSV and CMV.

EBV is an uncommon etiology of ARN, with a 2018 case report identifying only four other patients in the literature with a genomic diagnosis of EBV-ARN.^{13–17} One diagnostic challenge is the presence of latent EBV in the majority of healthy people, including 20% of human donor eyes,¹⁸ necessitating confirmatory negative testing of other known causes. Fortunately, PCR testing has approximately 95% sensitivity and specificity in detecting these viruses, allowing other potential viral etiologies to be ruled out.¹⁹ Other clinical signs of active EBV replication may help with the diagnosis, such as oral hairy leukoplakia.²⁰ In our case, the diagnosis of EBV-ARN in the second eye is supported by a vitreous sample positive for EBV and negative for HSV, VZV, and CMV, indicating that the second eye was infected independently of the VZV-ARN that affected the first eye.

EBV-ARN is less responsive to antiviral treatment, occurs almost exclusively in the immunocompromised, and is associated with worse visual outcomes compared to ARN caused by HSV or VZV.^{10,13} Poor visual outcomes from EBV-ARN may be due in part to its predilection for the posterior pole.¹³ While HSV- and VZV-ARN are characterized by predominant involvement of the peripheral retina with confluent spread, EBV-ARN is more likely to involve the macula with more marked occlusive arteriolaritis.¹³ These observations are consistent with the findings in our case, in which the eye affected by EBV-ARN demonstrated macular involvement and ultimately progressed to NLP vision. Systemic antiviral therapy, with oral valgacyclovir or intravenous acyclovir, accompanied by intravitreal foscarnet is recommended for ARN treatment in a 2017 report by the American Academy of Ophthalmology, although there is insufficient evidence to guide a particular treatment regimen for EBV-ARN.⁴

Our case has limitations. First, the aqueous sample from first eye was not tested for EBV. However, the positive VZV PCR result in the setting of recent clinical diagnosis of varicella zoster led to our diagnosis of VZV-ARN, and both eyes tested negative for HSV and CMV. Second, the etiology of the serous retinal detachment in the second eye may be multifactorial given its exudative appearance in a patient with multiple comorbidities (chronic VZV infection and severe renal disease), although the appearance of the retina was white and consistent with necrotizing retinitis. Our case also raises questions about duration of treatment of varicella zoster in the immunocompromised, as our patient developed symptoms of VZV-ARN about 3 weeks after completing 10 days of systemic therapy for dermatomal vesicular rash. Longer antiviral treatment protocols for immunocompromised patients with uncomplicated varicella zoster may be considered.²¹

3. Conclusion

In summary, we report a rare case of bilateral ARN with independent infection of each eye by different viruses; VZV affecting the left eye and, four months later, EBV the right eye. In addition to PCR evidence, the patient demonstrated clinical signs of systemic viral infection, with dermatomal vesicular rash preceding VZV-ARN and oral hairy leukoplakia at the time of presentation with EBV-ARN. Immunocompromised patients are vulnerable to ARN from any of its inciting viral causes, and intraocular fluid should be obtained for diagnostic confirmation at the time of second eye presentation in cases of bilateral ARN.

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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Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: AW, VN, BB, AE.

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