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Early Presentation of Successive Acute Retinal Necrosis Decades After Initial Infection

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Abstract

Purpose: To describe the early presentation of successive acute retinal necrosis (ARN) decades after the initial infection. **Methods:** A single case and its findings were analyzed. **Results:** A 62-year-old man with a remote history of left-sided ARN presented for evaluation of right-sided blurry vision. An examination showed 1+ anterior chamber cells and mild vitritis with multiple small patches of white retinitis. The lesions progressed despite treatment with oral antivirals, eventually requiring multiple doses of intravitreal antiviral agents and hospitalization for intravenous antiviral therapy. Despite a characteristic clinical picture consistent with ARN, multiple aqueous samples tested negative for viral etiologic agents. **Conclusions:** ARN is a rapidly progressive disease, and the diagnosis is clinical. Our patient was treated aggressively with antiviral therapy on the basis of the clinical picture without confirmatory testing, which remained negative. The lesions responded well to treatment and 20/25 visual acuity was maintained. Regardless of confirmatory testing, timely treatment is critical in cases of suspected ARN.

Keywords

acute retinal necrosis, uveitis, retinitis

Introduction

Acute retinal necrosis (ARN) is a rare, sight-threatening viral retinitis characterized by severe retinal necrosis. Untreated, the disease progresses rapidly, leading to irreversible retinal damage and potential blindness. Retinal detachment (RD) is the most common cause of decreased vision, with a reported incidence of 20% to 75% in treated eyes.[1] Bilateral ARN occurs in up to 70% of untreated patients.[2] Prompt diagnosis and management of ARN are crucial; however, the treatment approach remains challenging because of the varied etiology and clinical manifestations. The limited available evidence also makes the optimal treatment for ARN widely debated.

We describe a patient with a history of left-sided ARN who presented with right-sided ARN early in the disease course.

Case Report

A 62-year-old man presented reporting blurry vision and new floaters for the past few days in the right eye. His medical history included hypertension and multiple sclerosis in remission without ocular manifestations. On presentation, the patient was not receiving immunosuppressive medications. His ocular history was remarkable for left-eye phthisis attributed to hypotony subsequent to ARN more than 20 years ago. Although serology or a laboratory workup was not available, discharge reports showed that the patient was admitted for intravenous acyclovir treatment and was switched to intravenous ganciclovir for worsening kidney disease and leukopenia. Operative reports showed a history of pars plana vitrectomy (PPV), scleral buckling, fluid–air exchange, and endolaser treatment followed by multiple intravitreal (IVT) ganciclovir treatments. He then had complicated cataract surgery with anterior chamber intraocular lens placement complicated by pseudophakic bullous keratopathy and hypotony. The visual acuity (VA) in the left eye remained light perception (LP).

On examination, the patient's best-corrected VA (BCVA) was 20/25 OD and LP OS. The intraocular pressure (IOP) was 32 mm Hg and 19 mm Hg, respectively. An anterior segment examination showed 1+ anterior chamber cells and trace flare in the right eye. Mild vitritis and multiple small, discrete, white, flat, well-demarcated patches of retinitis along the inferior vascular

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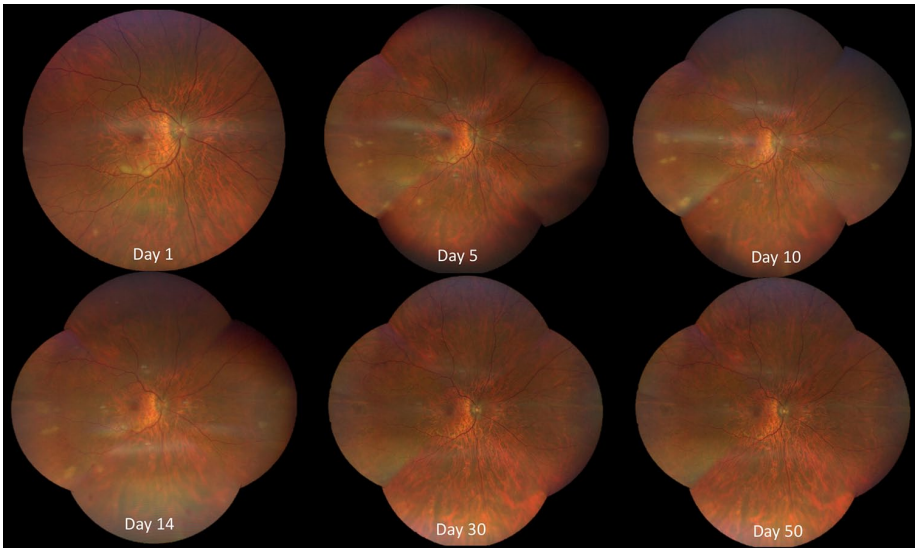

Figure 1. Widefield fundus photography of the right eye on day 1 shows multifocal areas of midperipheral inner retinal lesions along the inferior arcade. Subsequent follow-up on day 5 shows interval progression with more confluent and circumferential cream-colored lesions and hemorrhages along the arcades and periphery, despite treatment with high-dose oral valacyclovir. After initiation of intravenous acyclovir and intravitreal foscarnet, improvement is seen in all lesions and the vitreous inflammatory precipitates.

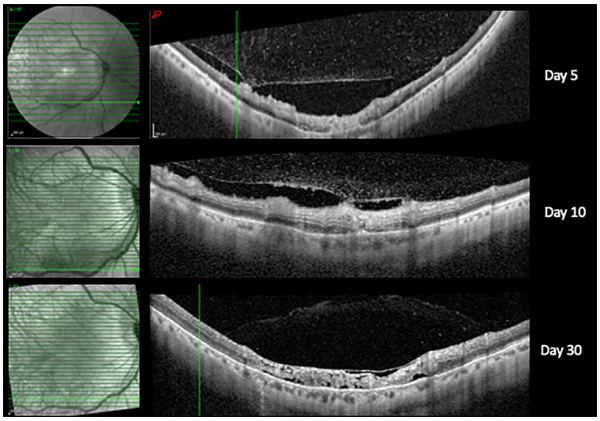

Figure 2. Optical coherence tomography shows associated mild posterior vitritis, subretinal fluid, and focal areas of thickening in the corresponding regions.

arcade were seen on the dilated fundus examination (Figure 1). Late peripheral hyperfluorescence along the veins without evidence of vaso-occlusion was seen on fluorescein angiography (FA), while optical coherence tomography (OCT) showed associated mild posterior vitritis, subretinal fluid (SRF), and corresponding areas of focal thickening (Figure 2).

Given the appearance of the lesions and the patient's history of previous ARN, oral valacyclovir 2 g 3 times a day was started for presumed early ARN; topical prednisolone, atropine, and IOP-lowering agents were also started. Laboratory testing for infectious and inflammatory etiologies was negative, although the patient was seropositive for herpes simplex virus 2 (HSV-2) immunoglobulin G (IgG) but negative for IgM. Anterior chamber aqueous was obtained and sent for polymerase chain reaction (PCR) testing for HSV-1 and HSV-2, varicella-zoster virus (VZV), cytomegalovirus (CMV), and toxoplasmosis. The patient's baseline renal function comprised an initial serum creatinine of 1.3 mg/dL and an estimated glomerular filtration rate of 62 mL/minute.

The patient was seen daily for the next 5 days. Oral valacyclovir was continued, and he also received 1 IVT injection of ganciclovir and 1 IVT injection of foscarnet. On the fifth day, despite therapy, the vitritis and anterior chamber inflammation worsened, with increasing areas of retinitis and the development of multiple new lesions. At that time, the results of the anterior chamber paracentesis studies had not been returned. Given that the patient was effectively monocular and his disease was worsening, he was admitted for intravenous antiviral treatment and an infectious diseases consultation.

The patient was started on intravenous acyclovir 10 mg/kg 3 times a day. HIV testing was obtained, as were blood cultures to rule out endogenous endophthalmitis, both of which were negative. The patient was admitted for 10 days, receiving 3 more IVT injections of foscarnet. While admitted, the patient's original aqueous PCR samples were reported as negative and a second sample was obtained. Throughout his admission, the patient's patches of retinitis initially increased in size and number, coalescing before eventually stabilizing and then decreasing in size. The BCVA decreased to a low of 20/100 before finally improving. Considering the improvement in the patient's examination, a decision was made to transition him to oral valacyclovir 2 g 3 times a day and discharge him with a plan for close follow-up. The serum creatinine ranged between 1.2 mg/dL and 1.4 mg/dL

over the course of the patient's admission, with the estimated glomerular filtration rate ranging from 57 to 68 mL/minute.

Before admission, the patient received 1 IVT ganciclovir 2.4 mg/mL injection and 1 full-dose foscarnet injection. Three full-dose foscarnet injections were administered while he was admitted, and 2 full-dose foscarnet injections and 3 half-dose foscarnet injections were administered after discharge, for a total of 10 IVT injections. Serial dilated fundus examinations showed the patient's retinitis was slowly resolving (Figure 1), and the BCVA in the right eye eventually returned to the baseline of 20/25. Repeat aqueous samples were again reported as negative. The patient's most recent (6 months after discharge) serum creatinine was 1.4 mg/dL. At the most recent follow-up, 97 days after initial presentation, the BCVA was 20/25 OD. No signs of active inflammation or evidence of retinitis were seen on slitlamp examination or dilated fundus examination.

Conclusions

ARN is a rare vision-threatening retinitis classically characterized by a panuveitis consisting of anterior segment inflammation, vitritis, and multiple foci of yellow–white retinal necrosis with associated vascular occlusion. Left untreated, ARN rapidly progresses to confluent necrosis and potentially RD.[1,3] It is commonly associated with VZV, HSV-1, and HSV-2, with some studies also implicating CMV and Epstein-Barr virus.[1,4,5] ARN is uncommon, with 2 population-based studies estimating incidences of 0.50 cases and 0.63 cases per million people, respectively.[4,6] For patients who develop ARN, however, the outcomes are often devastating, with multiple studies reporting roughly 50% of patients attaining long-term BCVA values of 20/200 or worse.[4,7] RD has been noted to occur in 20% to 55% of eyes, most within 180 days of initial presentation, despite a combination of oral, intravenous, and IVT antiviral agents, as well as prophylactic retinal photocoagulation in some studies.[4,7–10]

The American Uveitis Society established the original diagnostic criteria for ARN in 1984.[11] Although ARN is considered a clinical diagnosis, common ancillary testing techniques include viral PCR analysis of aqueous or vitreous samples as well as intravenous FA, OCT, and OCT angiography (OCTA). Most studies reported high rates (often greater than 80%) of positive PCR testing for HSV or VZV in cases of ARN, and there are no conclusive data showing that aqueous or vitreous sampling results in a higher diagnostic yield.[1] Intravenous FA can show arterial occlusion, peripheral nonperfusion, and leakage.[7,12] Vitritis and hyperreflective inner retinal deposits in the regions of necrosis as well as SRF are often seen on OCT, while OCTA can identify regions of nonperfusion.[13,14]

The mainstay of ARN treatment is early initiation of antiviral drugs, most commonly a combination of oral or intravenous therapy with or without IVT antiviral agents (foscarnet injections, 2.4 mg/0.1 mL) or ganciclovir (200 to 2000 μg/0.1 mL).[1,15,16] The aim of systemic treatment is not only to preserve some degree of vision in the affected eye but also to prevent sequential ARN in the fellow eye, which has been shown to develop in a significant proportion of untreated eyes.[4,7] Most cases of bilateral ARN develop within months of initial presentation, although there are reports of sequential ARN developing decades later.[17,18] Historically, induction treatment consisted of intravenous acyclovir (10 mg/kg for 7 to 10 days) before initiating oral antiviral agents, as supported by level III evidence (well-designed controlled trials without randomization).[1] The introduction of the prodrug valacyclovir allowed for the attainment of comparable serum drug levels using oral dosing.[1,19] Studies have found similar average serum levels and area under-the-curve values when comparing intravenous acyclovir and oral valacyclovir, although the use of intravenous acyclovir provides the highest serum concentration more quickly and results in a higher maximum drug level.[1]

The choice of intravenous vs oral antiviral induction therapy is not clear-cut. Some case series and recent retrospective studies have found good outcomes using only oral valacyclovir (often 1 g 3 times a day) as induction therapy. However, some sources suggest using valacyclovir 2 g 4 times a day, which might allow for serum drug concentrations closer to intravenous acyclovir induction.[20–23] A recent meta-analysis reported no difference in VA improvement between patients treated with induction intravenous vs oral antiviral agents alone. Of note, the authors found a nonsignificant trend toward increased VA improvement when comparing combination systemic and IVT treatment with intravenous or oral treatment alone.[19] Flaxel et al[24] compared 14 eyes treated with combined systemic and IVT antivirals with 15 eyes that received systemic therapy only and found that patients in the combination group were significantly more likely to have an improvement in VA and a lower incidence of RD.

The use of corticosteroids and laser retinopexy in ARN remains controversial. Several retrospective studies suggest that early steroid use can prevent RD and improve visual outcomes, while others have noted that steroid use could increase viral replication and worsen disease. Shantha et al[5] found that patients with ARN who started corticosteroids within 72 hours of systemic antivirals had significantly better VA than those who started later or not at all. Wong et al[12] observed better long-term conservation of VA in patients treated with corticosteroids and antiviral agents than those treated with antiviral agents alone. However, Dorman and Donaldson[3] found no difference in the risk for RD or severe vision loss between patients who received systemic corticosteroids and those who did not.

First described in 1987, laser retinopexy for the prevention of ARN-associated RD involves applying laser photocoagulation to create chorioretinal adhesions surrounding the areas of necrotic retina that are prone to developing breaks.[1,8,25] Some small case series reported a reduction in the incidence of RD with prophylactic laser treatment, although many are limited by sample size and selection bias (excluding severe vitritis or advanced retinitis cases), with an overall marginal benefit reported.[1,8,26] Other studies found no benefit, with some authors suggesting that laser treatment could worsen inflammation or traction.[1,3,27] A 2022 meta-analysis of 14 studies that included

532 eyes found that laser photocoagulation significantly reduced the risk for detachment, especially in combination with antiviral and steroid therapy.[28]

Surgical therapy, often PPV with or without silicone oil tamponade, may be necessary to repair ARN-associated RDs.[27,29] Prophylactic vitrectomy is controversial, with some arguing that releasing traction to areas of retinal necrosis might decrease the risk for detachment and lessen the inflammatory burden.[1] Prophylactic vitrectomy when ARN was active appeared to lower the incidence of RD from 45% to 22%; however, the difference was not statistically significant. In the same meta-analysis, systemic antiviral therapy plus vitrectomy lowered the rate of RD to 18%, although this decrease was not significant.[30]

Our patient's case emphasizes several points. First, ARN is a clinical diagnosis, and prompt treatment should be initiated based on clinical judgment. This case can be considered "atypical ARN" in multiple respects. Not only did the patient present early in the disease course when the characteristic retinal lesions were less confluent and smaller in size and number, but multiple anterior chamber PCR tests were negative for HSV-1 and HSV-2 and VZV. Despite these factors, the clinical picture was consistent with ARN and prompted the decision to treat. Systemic treatment with oral antivirals may be insufficient, as seen in this patient, and intravenous antivirals as well as IVT treatment should be considered. In addition, this case emphasizes the importance of maintaining a high degree of suspicion for ARN in patients with even a remote history in the opposite eye because sequential infection can occur decades after a contralateral diagnosis.

In conclusion, we present a challenging case of PCR-negative ARN in a monocular patient with a remote history of ARN in the fellow eye. ARN is a clinical diagnosis, and treatment should not be delayed while awaiting positive PCR test results.

Ethical Approval

Ethical approval was not sought for the present study because it was exempt and no patient-identifying information was included.

Statement of Informed Consent

Written informed consent was not sought for the present study because no patient-identifying information was included.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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