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Acute Retinal Necrosis with Multiple Viral Infections: A Case Report

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Abstract

A 52-year-old male presented with acute retinal necrosis in his left eye. Slit lamp examination revealed stellate keratic precipitates and cells in the anterior chamber and vitreous. Funduscopy of his left eye revealed multiple yellow deposits. Pathological examination of the vitreous showed both small, reactive lymphocytes and a few macrophages. IL-6 and IFN- γ were elevated in the vitreous. Microdissected macrophages from the vitreous revealed DNAs from multiple viruses. The patient responded to oral valacyclovir. We conclude that multiple viral infections can be involved in the pathogenesis of acute retinal necrosis and that adequate anti-viral therapy has a beneficial effect on disease progression. However, retinal detachment can be a consequence for a poor visual outcome.

Keywords

Acute retinal necrosis; Viral infection; Anti-viral treatment

Introduction

Acute retinal necrosis (ARN) is characterized by progressive intraretinal inflammation and necrosis. ARN is often unilateral and is associated with retinitis and panuveitis. Clinically, the disease is characterized by anterior uveitis, vitritis, retinal necrosis beginning in the peripheral retina, and occlusive vasculitis involving the retina and choroid [1,2]. It has been suggested that the pathogenesis is closely tied to viral infection, most commonly with varicella-zoster virus (VZV) and herpes simplex virus (HSV), though there are some cases where the infectious agent has been cytomegalovirus (CMV) or Epstein-Barr virus (EBV) [3]. Although EBV infection in ARN is rarely found alone, but rather co-existing with VZV infection [4], a recent report has demonstrated EBV as the only virus in the retina of a patient with ARN [5]. The most common therapeutic approach for ARN is anti-viral therapy

immediately after diagnosis [2]; in previous reports, early vitrectomy with intravitreal lavage using anti-viral medication was associated with a lower incidence of secondary retinal detachment [3]. Herein, we report a case of ARN with multiple herpetic viral infections, which were confirmed by the detection of viral DNA in the macrophages found in the vitreous. The patient was treated with oral valacyclovir and responded to the therapy.

Case History

A 52-year-old male presented with ocular discomfort and increased conjunctival injection in his left eye. On March 8, 2014, ocular examination of his left eye revealed a visual acuity of 20/25, and the anterior segment showed 2+ flares and 2+ fine cells. Slit lamp examination revealed stellate keratic precipitates in the inferior section of the cornea and vitreal haze with a moderate number of cellular infiltrates. Fundus examination was notable for blurring of the nasal aspect of the optic nerve. There were also multiple small yellow deposits circumferentially in the periphery at the level of the deep retina (and possibly with choroidal involvement) with larger deposits both nasally and superiorly. There was moderate tortuosity of the veins and evidence of vasculitis. Ocular examination of the right eye was unremarkable. On March 19, 2014, ocular examination revealed that the chorioretinal infiltrates had increased in size; laboratory evaluation demonstrated mild elevation of the HSV IgG and IgM, VZV IgG, and a positive ANA. At this point, a clinical diagnosis of acute retinal necrosis was considered, and the patient was prescribed 1 gram of valacyclovir 3 times per day by mouth. On March 21, 2014, the clinical symptoms had improved with decreased ocular discomfort. Slit lamp examination showed a normal anterior segment and minimal vitritis. Fundus examination showed coalescence and continued enlargement of the chorioretinal lesions circumferentially. Oral valacyclovir was increased to 2 grams 3 times per day. A diagnostic vitrectomy was performed in the left eye on March 27, 2014. The specimen was sent for pathology.

On April 4, the fundus examination showed no progression of the necrotic area since the last examination; however, there were still round, discrete areas of chorioretinal involvement in almost every quadrant. There was also coalescence of the previously seen chorioretinal scars (Figure 1). A fundus examination on May 2, 2014 showed some regression of previous chorioretinal lesions and inflammation in various portions of his peripheral retina. The inflammatory appearance of the retinal arteries had also decreased (Figure 2). His visual acuity was 20/50. Thus, the patient's dose of valacyclovir was lowered to 1 gram 3 times per day.

The patient was stable for 4 months. On August 6, 2014, he developed a sudden onset of vision loss. Ocular examination showed a macular detachment. Scleral buckling and vitrectomy were performed successfully. However, his vision remained poor: count finger to hand movement.

Pathological Examination of the Vitreous

Examination of the vitreous discloses small and reactive lymphocytes, a few macrophages, and significant amounts of debris (Figure 3). The level of the IL-6 in the vitreous was 285.0

pg/mL, and IFN- γ was 202.6 pg/mL as measured by enzyme-linked immunosorbent assay (ELISA). Macrophages were microdissected for molecular analysis. The primer pair (Forward: 5'-GTGGTGGACTTTGCCAGCCTGTACCC-3; Reverse: 5'-TAAACATGGAGTCCGTGTCGCCGTAGATGA-3), which can identify the presence of HSV-1, HSV-2, EBV, or CMV, and the primer pair (Forward: 5'-GTCGTGTTTGATTTTCAAAGTTTATATCC-3; Reverse: 5'-ATAAACACACAATCCGTATCACCATAAATAACCT-3), which can identify VZV, HHV-6, or HHV-7, were used in polymerase chain reaction (PCR) to determine the presence or absence of viral DNA in the microdissected macrophages [6]. Both primer pairs amplified, indicating the presence of at least two different viral infections (Figure 4).

Discussion

In this case, we confirmed the diagnosis of ARN by herpetic viruses based on PCR. We also found high levels of IFN- γ and IL-6 in the vitreous. IFN- γ is not only a cytokine that is released by Th1 and natural killer (NK) cells but also has anti-viral function [7]. Furthermore, both HSV-1 and HSV-2 are potent inducers of IL-6, and this phenomenon is augmented in the presence of IFN- γ [8]. The amplification of viral DNA by PCR further augments this hypothesis. Therefore, the elevated level of IFN- γ and IL-6 may reflect a systemic response to the viral infection. Since HHV-6 and HHV-7 have been proven to not be implicated in the pathogenesis of ARN, furthermore CMV rarely induces ARN [4], HSV and VZV are most likely the viruses infecting the eye of this patient. Serum HSV IgG and VZV IgG titles also support the co-infection of HSV and VZV.

Treatment for ARN is based on the detection of viral DNA in the vitreous biopsy. Prompt treatment with intravenous acyclovir and systemic corticosteroids is recommended. However, intravitreal ganciclovir or foscarnet combined with oral famciclovir or valacyclovir and oral corticosteroids has also been prescribed with significant benefit [9]. One study investigating the use of oral anti-viral medications valacyclovir and famciclovir as the only treatment for ARN with a mean follow-up of 36 weeks and found that active retinitis resolved completely without involvement of the contralateral eye [9]. In our case, only oral valacyclovir was promptly given, and the patient responded well with the lesions becoming inactive and stable, emphasizing the importance of early anti-viral treatment in ARN [10].

Retinal detachment following ARN is well documented in multiple studies. Clarkson and colleagues reported in 1984 that 16 of 32 eyes (50%) with ARN developed retinal detachment. Surgical repair was performed in 13 eyes, of which 10 retinas were successfully reattached [11]. In a series of 25 ARN eyes, retinal detachment occurred in 20% (5 eyes), and the average time from the symptom onset to retinal detachment was 65 days [12]. A multicenter retrospective, interventional series of 58 patients with unilateral ARN found that 29/58 (50%) patients developed retinal detachment. No variables significantly predicted or prevented the risk of retinal detachment, including prophylactic laser photocoagulation [13]. In a recent retrospective study of 62 ARN eyes which received prompt antiviral therapy, 41 eyes (66.12%) developed retinal detachment and 32 eyes (51.61%) required surgical repair [14]. As expected, the eyes without retinal detachment resolved with better vision when

compared to eyes with detachment; however, the difference was not statistically significant if the detachment is immediately and successfully repaired.

In summary, this case represents a typical ARN case with multiple deep retinal infiltrates and vasculitis due to HSV and VZV infection. Clinical, pathological, and molecular data are well illustrated, and it supports the use of a single oral anti-viral medication in the early treatment of ARN.

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Figure 1. Fundus photograph of the left eye. (A) Vitreous haze. (B) Nasal blurred optic disc margin and retinal vasculitis (black arrows). (C) Large retinal infiltrates (white arrows) at the peripheral area. (D) Small yellow lesions (white arrows) at the peripheral retina.

Figure 2. Fluorescent angiogram of the left eye. (A) Before anti-viral medication, (B) After anti-viral medication.

Figure 3.
Vitreous cytology. The specimen is composed of lymphocytes, macrophages and debris.
(Giemsa, original magnification, x400).

Figure 4. PCR products of viral DNA after gel electrophoresis. Primer 1: primer pairs for detecting HSV-1, HSV-2, EBV, CMV; Primer 2: primer pairs for detecting VAV, HHV-6, and HHV-7. N: negative; P: positive.