Case series: Two cases of herpetic retinitis presenting as progressive outer retinal necrosis in immunocompetent individuals

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ABSTRACT

Purpose: To raise awareness of ophthalmologists that Varicella Zoster Virus (VZV) retinitis should be considered in the differential diagnosis of retinitis that presents with features of progressive outer retinal necrosis (PORN) in healthy immunocompetent patients.

Observations: Case 1 is a 39-year-old healthy Caucasian male who presented after one week of decreased vision in the left eye. Patient was found to have optic disc edema and multifocal retinitis primarily localized to the posterior pole with only a few lesions in the periphery and minimal vitritis. Viral PCR of a vitreous tap was positive for 1 million copies of VZV. Patient ultimately progressed to no light perception vision despite multiple intravitreal injections of foscarnet and several days of intravenous acyclovir therapy. Case 2 is another 39-year-old healthy Caucasian male that presented after 2 weeks of decreased vision in the left eye. On initial exam by his primary ophthalmologist, patient was found to have optic disc edema and multifocal retinitis primarily localized to the posterior pole with no peripheral lesions and no vitritis. The patient then presented to our clinic with extensive retinitis throughout the posterior pole and periphery, and he underwent a vitreous tap with viral PCR positive for 3160 copies of VZV. He was treated with intravitreal injections of foscarnet and intravenous acyclovir therapy with subtle progression to the right eye and only minimal improvement of left eye vision to 20/200.

Conclusions and Importance: Progressive outer retinal necrosis (PORN) is a herpetic retinopathy characterized by rapidly progressive necrosis of the outer retina in severely immunocompromised subjects. As demonstrated in this case series, VZV retinitis should be considered as a differential diagnosis in patients with hallmark features of PORN, even in the absence of obvious systemic immunosuppression.

1. Introduction

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) represent two variants of rapidly progressing necrotizing herpetic retinitis, each with distinctly different features. The Executive Committee of the American Uveitis Society characterizes ARN as a peripheral necrotizing retinitis and occlusive retinal arteritis with a prominent inflammatory reaction in the vitreous and anterior chamber. It can occur in both immunocompromised and immunocompetent individuals. By contrast, PORN has been described almost exclusively in immunocompromised persons, such as those infected with HIV/AIDS or otherwise immunosuppressed. The clinical features of PORN that distinguish it from ARN include early involvement of necrotizing lesions in the posterior pole and macula, little to no intraocular inflammation, and minimal vasculopathy. The etiology of both conditions involves reactivation of a latent herpetic infection, varicella zoster virus (VZV) being the most common cause, followed by herpes simplex virus (HSV) types 1 and 2.

Here we report two unique cases of healthy adults that presented with necrotizing herpetic retinitis with hallmark features of PORN. In each case, there was a delay in care due the atypical presentation in patients without known immunosuppression.

2. Findings

2.1. Case 1

A 39-year-old Caucasian male presented with a one-week history of eye pain and decreased vision in the left eye. The patient was incarcerated at this time and seen by a physician in the federal facility who
initiated treatment with artificial tears. The patient’s only known medical history included hypertension. His past ocular history, surgical history and family history were non-contributory. Visual acuity was 20/20 in the right eye, and light perception only in the left eye. There was a positive relative afferent pupillary defect in the left eye. Intraocular pressures by applanation tonometry were 19 mmHg and 50 mmHg in the right and left eye, respectively. Examination of the unaffected right eye was normal. Examination of the left eye revealed a clear cornea and 2+ anterior chamber cells. Dilated fundus exam of the left eye showed trace vitritis, grade-4 disc edema with peripapillary hemorrhages, and multifocal retinitis primarily localized to the macula and posterior pole with only a few lesions in the mid-periphery (Fig. 1A). Fluorescein angiogram (FA) of the left eye was consistent with early areas of blocked fluorescence in the macula, followed by late leakage from the disc and minimal leakage from retinal vessels in the inferior arcade (Fig. 1B). Indocyanine green angiography (ICG) of the left eye revealed mild blockage in the macula and few areas in the posterior pole and mid-periphery (Fig. 1C). Optical coherence tomography (OCT) examination of the macula in the left eye revealed cystoid macular edema (Fig. 1D). Right eye FA, ICG and OCT of the macula were non-revealing.

The patient denied recent travel, high-risk sexual behavior, recent tick bites, previous eye surgery or trauma, and intravenous drug use. HIV screen, T-spot, and Syphilis IgG were negative, and CD4 count was normal. Viral quantitative polymerase chain reaction of a vitreous tap was positive for 1 million copies of varicella zoster virus (VZV). He received intravitreal foscarnet (2.4mg in 0.1 mL) followed by anterior chamber paracentesis which normalized the intraocular pressure. The patient was started on 2 g of oral valacyclovir four times daily with frequent topical steroid drops. At follow-up 48 hours later, he had progressed to no light perception vision in the left eye, and exam was otherwise stable. At this time the patient received re-injection with foscarnet and admission to the hospital for intravenous acyclovir (15mg/kg every 8 hours). He was also started on atropine drops and dorzolamide-timolol eye drops twice a day for high intraocular pressure. After 48 hours of hospitalization, intravenous solumedrol (250mg every 6 hours) was started and continued for 5 days. The patient completed 7 days of intravenous acyclovir, and was discharged back to the federal facility on 2 g of oral valacyclovir four times a day for 7 days, followed by 2 g three times a day for 30 days.

At one-month follow-up, visual acuity was still 20/20 in the right eye and no light perception in the left eye. Fundus exam of the right eye was unremarkable, and the left eye revealed optic disc pallor with resolving retinitis (Fig. 1E). OCT of the macula in the left eye showed resolution of macular edema (Fig. 1F). Oral valacyclovir was decreased to 1 g three times a day.

2.2. Case 2

A 39-year-old Caucasian male initially presented to an outside general ophthalmologist with the complaint of decreased vision in the left eye. His exam demonstrated grade-2 disc edema concerning for optic neuritis. Over the next two weeks the patient developed retinal lesions mainly throughout the posterior pole, consistent with retinitis (Fig. 2A–B). At this time, the patient was started on topical steroid drops and atropine drops and referred to our clinic for evaluation. Associated medical conditions only included hypertension. His past ocular history, surgical history, and family history were non-contributory. The patient denied recent travel, high-risk sexual behavior, recent tick bites, previous eye surgery or trauma, and intravenous drug use. An HIV screen, Syphilis IgG, and purified protein derivative (PPD) tests were negative. At the time of presentation to our clinic, visual acuity was 20/20 in the right eye and count fingers at 5 feet in the left eye. There was a positive relative afferent pupillary defect in the left eye. Intraocular pressures by applanation tonometry were 19 mmHg and 24 mmHg in the right and left eye, respectively. Examination of the unaffected right eye was normal (Fig. 2D). OCT of the macula in the left eye revealed cystoid macular edema (Fig. 2F). Examination of the left eye revealed 2+ cells in the anterior chamber, minimal vitritis, grade-3 disc edema, and multifocal retinitis throughout posterior pole, periphery and macula with sparing of the fovea (Fig. 2C). OCT of the macula in the left eye revealed subretinal fluid superonasal to the fovea. (Fig. 2D). OCT of the right eye was normal. A vitreous tap was performed, and the patient received an intravitreal injection of foscarnet (2.4mg in 0.1 mL) and was started on 2 g of oral valacyclovir four times daily with frequent topical steroid drops. Viral quantitative polymerase chain reaction of the vitreous tap was positive for 3160 copies of VZV.

The patient followed up 4 days later and visual acuity was 20/20 in the right eye and hand motion in the left eye. Anterior segment exam was stable for both eyes. Dilated fundus exam revealed healing retinitis in the left eye (Fig. 2E), and new retinitis lesion along the superior arcade in the right eye (Fig. 2G). OCT of the left eye was stable and OCT of the right eye was normal, without any evidence of intraretinal or subretinal fluid. The patient was then admitted to the hospital for intravenous acyclovir (15mg/kg every 8 hours).

During the hospital course, the patient experienced an acute kidney

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**Fig. 1.** Panel A: Color fundus photograph of left eye revealing grade-4 disc edema with peripapillary hemorrhages and multifocal retinitis primarily localized to the macula and posterior pole, with few lesions in the mid-periphery. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
injury due to the high dose of acyclovir, and dosage was then adjusted and decreased based on kidney function. The patient then developed another small retinal lesion in the periphery in the right eye (Fig. 2 H–J), with stable fundus appearance in the left eye. Intravitreal antiviral therapy for the right eye was discussed at this time, in which the patient declined and wanted to continue intravenous therapy instead. After 10 days of hospitalization, the patient was discharged on 2 g of oral valacyclovir three times daily. At clinic follow-up one week later, visual acuity was 20/20 in the right eye and 20/200 in the left eye. Dilated fundus exam demonstrated resolving retinal lesions in the right eye and worsening vitritis in the left eye for which an additional intravitreal injection of foscarnet (2.4mg in 0.1 mL) was given. Oral corticosteroids were later added, and he was continued on valaciclovir with slow regression of the left eye retinitis.

3. Discussion

The cases presented are of particular interest due to their atypical clinical presentation. Both patients were young healthy adults presenting with sudden onset of optic disc edema, retinitis throughout the macula and posterior pole, and minimal vitreous inflammation - clinical features consistent with PORN and most often seen in immunosuppressed patients. However, neither patient showed signs of immunosuppression. Thus, there was a delay in the care and proper diagnosis in both patients. A high dose of oral valacyclovir 2 g four times daily was given to each patient as an attempt to achieve serum concentration similar to that achieved with intravenous acyclovir. In addition, each patient was started on oral prednisone afterwards as delayed use of corticosteroids have been shown to possibly have a role when the optic disc is involved.5

To our knowledge, there is only one similar case in the literature that describes PORN in an immunocompetent subject. In 1996, Carrillo-

Fig. 2. Panel A–B: Initial color fundus photographs obtained by the referring ophthalmologist of the left eye revealing grade-2 disc edema and multifocal retinitis confined to the superior arcade and posterior pole. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
Pacheco et al. published the case of an immunocompetent adolescent that presented with bilateral ophthalmic findings of multifocal retinitis throughout the macula and mid-periphery with minimal intraocular inflammation. The ability to obtain viral PCR from a vitreous sample was likely not available at this time, but the diagnosis was presumed to be PORN based on a positive serum fluorescent-antibody-to-membrane-antigen (FAMA) test for VZV and clinical improvement with intravenous acyclovir.

Another case series in 2003 reported two patients over the age of 55 considered to be immunocompetent with findings consistent with PORN after being treated with high-dose corticosteroids for presumed optic neuropathy. However, it is most likely that the immune status of these patients was compromised by the systemic corticosteroid treatment. In addition to high dose corticosteroids therapy, one patient was on long-term therapy for rheumatoid arthritis with anti-TNF, etanercept, while the other patient had a known diagnosis of multiple sclerosis and it was not mentioned if there was concurrent systemic treatment for this.

Necrotizing herpetic retinitis comprises a spectrum of disease induced by latent reactivation of a herpes viruses with the resulting clinical picture depending on the host immune state. At one end of the spectrum, patients with non-detectable or slight immune dysfunction clinically present with features classic for ARN. On the other end of the spectrum, the clinical features of PORN are seen almost exclusively in severely immunosuppressed patients. Clinically, the posterior pole presentation and involvement of the outer retina initially is what led to suspect the diagnosis of PORN in our patients. In addition, the outer retinal damage seen on the OCT in Figs. 1F and 2D is characteristic of PORN. This is in contrast to the full thickness necrosis typically seen in ARN. The cases we have presented support the possibility that there may exist intermediary forms between these extremes.

4. Conclusions

The cases presented demonstrate the possibility that retinitis with clinical features consistent with PORN can present in patients even in the absence of immunosuppression, and that an intermediate form of necrotizing retinopathy may exist. Therefore, diagnosis and treatment of a PORN-like retinitis should not be delayed on the basis of the patient’s immune status.

Patient consent

The patients consented to publication of the case in writing.

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