Rapidly Progressive Outer Retinal Necrosis Caused by Varicella Zoster Virus in a Patient Infected with Human Immunodeficiency Virus

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We describe a 21-year-old immunocompromised patient with a unique type of necrotizing herpetic retinitis. The retinitis progressed with loss of vision when acyclovir or ganciclovir alone was used for treatment. Examination of a chorioretinal biopsy specimen revealed that varicella zoster virus was the causative agent. Foscarnet monotherapy also failed to prevent progression of the retinal infection. Combination antiviral therapy with ganciclovir and foscarnet appeared to delay progression of disease and helped maintain a visual acuity of 20/200 for at least 6 months after the onset of infection.

Case Report

A 21-year-old man who had hemophilia and was infected with HIV presented with decreased peripheral vision of 2 days' duration in the left eye. His medical history was significant for varicella acquired 3 months prior to presentation after exposure to a sibling with chickenpox. Ocular examination revealed a visual acuity of 20/20 in both eyes. Examination of the right eye showed a normal anterior segment and fundus. Examination of the left eye revealed a normal anterior segment without inflammation. Funduscopic examination of the left eye showed complete whitening of the retinal periphery with an edge consisting of multiple white plaques that advanced toward the fovea (figure 1). Outer retinal necrosis or atypical cytomegalo-virus (CMV) retinitis was diagnosed. The patient started treatment with ganciclovir (induction dose, 5 mg/kg every 12 hours). Serum titers of antibodies to herpes simplex virus (HSV), CMV, and VZV were negative.

After 11 days of ganciclovir therapy, the patient was readmitted because of an acute intracranial hemorrhage. Ganciclovir was replaced with intravenous acyclovir (500 mg/m² every 8 hours) to prevent pancytopenia. After 1 week he was discharged with a prescription for oral acyclovir (800 mg five times a day).

Four weeks later the retina of the left eye became detached. The retinal detachment was surgically repaired, and acyclovir therapy was continued. Despite antiviral therapy, the retinitis continued to progress within the retinal vascular arcades (figure 2) and ultimately involved the entire retina. A vitrectomy with a chorioretinal biopsy was performed. The tissue was submitted to the laboratory for routine cultures as well as specific cultures for HSV and VZV. All studies were negative except the culture for VZV. To isolate VZV, tissue was inoculated onto culture media containing human lung fibroblast cells (MRC-5); there was definite growth after 7 days. Immunoﬂuorescent identification was performed by staining the cells with monoclonal antibodies specific for VZV glycoproteins with use of the Ortho Varicella-Zoster Virus Identification Reagent (Ortho Diagnostic Systems, Raritan, NJ).

Three weeks later, while the patient was still taking oral acyclovir, the same process developed in the periphery of the right eye. Acyclovir therapy was discontinued, and treatment with foscarnet (induction dose, 60 mg/kg every 8 hours) was started. One week later, while the patient was taking foscarnet, new lesions developed (figure 3). Ganciclovir (induction dose, 5 mg/kg every 12 hours) was added to the regimen. After 2 weeks, combination induction therapy was converted to maintenance therapy with ganciclovir (5 mg/kg daily) and foscarnet (90 mg/kg daily). Progression of the retinitis was temporarily halted. Visual acuity remained stable at 20/20 in the right eye for the following 12 weeks. Ultimately, the retinitis progressed to involve the fovea, which resulted in a best corrected visual acuity of 20/200. On the patient's last ocular examination, 6 months after the onset of retinitis in the right eye, the visual acuity remained stable at 20/200.
acuity in the right eye remained stable at 20/200. The patient died 3 months later with end-stage AIDS.

Discussion

The syndrome of rapidly progressive outer retinal necrosis is a unique type of necrotizing herpetic retinitis. The diagnosis is based on clinical findings [3]. The diagnostic criteria include the presence of multifocal lesions without granular borders in the deep retinal layers, evidence that the infection started in the peripheral retina with or without foveal involvement, an extremely rapid progression, and the presence of minimal intraocular inflammation [4].

Rapidly progressive outer retinal necrosis is commonly compared to acute retinal necrosis (ARN) syndrome because of some shared similarities. The herpesviruses have been implicated as the causative agents in both of these retinal infections [5-7]. Both syndromes have a predilection for starting in the peripheral retina. However, rapidly progressive outer retinal necrosis has been described only in immunocompromised patients [4, 8], while ARN has been described in both immunocompromised and immunocompetent individuals [9]. In addition, one of the key distinguishing features between rapidly progressive outer retinal necrosis and ARN is the relative absence of intraocular inflammation in the former syndrome. Thus, pain, which is a common presenting symptom in patients with ARN, is usually not found in patients with rapidly progressive outer retinal necrosis syndrome. The most common presenting symptoms in rapidly progressive outer retinal necrosis are decreased vision and/or a constricted peripheral visual field [4].

At present there is no effective treatment for rapidly progressive outer retinal necrosis. The increasing evidence implicating VZV as the cause of this infection has led to the logical selection of acyclovir as the drug of choice. Acyclovir, like ganciclovir and foscarnet, is efficacious against HSV and VZV. However, acyclovir is far less toxic than are the latter two antiviral agents. In patients with AIDS for whom bone marrow suppression and renal insufficiency are common problems, acyclovir therapy provides a relatively safe alternative treatment. However, the clinical outcomes in patients treated exclusively with acyclovir remain poor. The majority of cases culminate with vision that ranges from perception of hand motion to no light perception [4]. Treatment with ganciclovir or foscarnet alone has also been disappointing. The poor visual outcomes for patients treated with these

Figure 1. Fundal photograph (left eye) of the inferior nasal quadrant of a hemophilic, HIV-infected patient with rapidly progressive outer retinal necrosis showing an area of confluent retinal whitening with a posterior border consisting of multiple discrete areas of retinal opacification.

Figure 2. Fundal photograph (left eye) showing 360° of retinal whitening within the temporal vascular arcades.

Figure 3. Fundal photograph (right eye) showing multiple areas of retinal opacification encroaching upon the fovea.
agents are primarily due to progression of the retinitis despite the use of antiviral therapy, to involvement of the optic nerve, and to the relatively high number of retinal detachments.

The use of laboratory tests to identify the etiologic agent of rapidly progressive outer retinal necrosis has also been discouraging. As is the case with ARN, laboratory tests in cases of outer retinal necrosis are frequently negative despite the clinical evidence of infection [10]. In our case the patient was known to have had chickenpox and had positive retinal cultures for VZV, yet titers of antibody to varicella were negative. This difficulty in obtaining positive confirmatory test results has led to the sparsity of culture-proven cases of rapidly progressive outer retinal necrosis despite the relatively large number of reported cases [4, 8].

The findings in our report add to the growing body of literature that supports VZV as a causative agent of the syndrome of rapidly progressive outer retinal necrosis. In addition, we cite our experience with combination drug therapy for the treatment of this herpetic retinitis.

The use of combination antiviral therapy is not a novel approach in the management of herpetic viral infections. Ganciclovir and foscarnet are both efficacious in the treatment of herpetic viral infections, and there is evidence that synergism exists between ganciclovir and foscarnet [11]. In our case, the use of antiviral monotherapy failed to halt progression of the retinitis. There was rapid visual loss in the patient’s left eye with the use of acyclovir or ganciclovir alone. Foscarnet monotherapy also resulted in progression of the retinal infection in the right eye. The use of combination therapy with ganciclovir and foscarnet did appear to significantly delay progression of disease in the right eye and maintain a visual acuity of 20/200 for at least 6 months after the onset of the retinitis. Given the poor visual outcomes with standard monotherapy and the rapid progression of this disease, it may be appropriate to initiate treatment with combination drug therapy as soon as the diagnosis is made.

References