Rapidly Progressive Herpetic Retinal Necrosis: A Blinding Disease Characteristic of Advanced AIDS

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Eleven patients with rapidly progressive herpetic retinal necrosis (RPHRN) complicating AIDS were investigated retrospectively to study the disease spectrum, systemic involvement, and therapy. The mean CD4 cell count was 24/μL. There was a characteristic disease pattern with rapid progression, 82% bilaterality, relative resistance to intravenous antiviral therapy, and 70% retinal detachment. Varicella-zoster virus was the probable cause in 10 patients (detected by polymerase chain reaction in two eyes investigated), and herpes simplex virus was the probable cause in one. Cutaneous zoster occurred previously in 73% but was not concurrent. Seventy-three percent had central nervous system disease, possibly virus-related. RPHRN may be a local herpetic recrudescence in an immune-privileged site with transneural spread. Only four of 20 affected eyes retained useful vision. Poor ocular bioavailability, retinal ischemia, acquired drug resistance, and strain pathogenicity may underlie treatment failure. Acyclovir therapy appears relatively ineffective. Combined intravenous and intravitreal therapy with foscarnet and ganciclovir may be the best current management. Research advances are needed urgently.

The blinding complications of AIDS are particularly feared. Patients in the late stages of HIV infection, many already debilitated with intercurrent infections or tumors, are confronted unexpectedly with sudden visual loss in one or both eyes. Furthermore, immunosuppression and the ocular pharmacokinetics of currently available drugs commit most of these patients to intravenous therapy for the remainder of their lives.

Cytomegalovirus (CMV) retinitis remains by far the most common ocular opportunistic infection to involve the eye; its clinical pattern and behavior are quite distinct and easily differentiated on clinical grounds from other causes of viral retinitis [1]. Increasingly, varicella-zoster virus (VZV) and herpes simplex virus (HSV) retinitis is occurring in AIDS patients, usually with a unique disease pattern and described as rapidly progressive herpetic retinal necrosis (RPHRN) or, less accurately, as progressive outer retinal necrosis (PORN) syndrome [2–5]. This newly recognized disease was first described in 1990 [2] and has a very poor visual prognosis with current management.


Retinitis caused by the herpesviruses is generally uncommon [3–6]. There has been no consistent agreement until recently as to the definition of the various herpetic retinitis syndromes [7]. Acute retinal necrosis (ARN) is the most common clinical syndrome in immunocompetent individuals, usually caused by VZV [3, 4, 8, 9] and characterized by focal, well-demarcated areas of necrotizing retinitis involving the retinal periphery anterior to the retinal vascular arcades. ARN has a marked tendency to circumferential progression, an associated occlusive retinal vasculitis, prominent vitritis, and symptomatic anterior uveitis [7]. Although most patients initially have unilateral disease, subsequent bilateral involvement is common. HSV can produce a similar ARN syndrome, although more often in association with viral encephalitis [5]. Atypical cases of herpetic retinitis that fulfill some but not all of the diagnostic criteria are described as necrotizing herpetic retinopathy, rather than ARN, and the word presumed is added when appropriate [7].

Intravenous acyclovir treatment in ARN induces clinical improvement in 48–72 hours [4, 8, 9]. Untreated, ARN begins to regress spontaneously in 3–4 weeks and usually does not extend into the macula. However, the involved retina becomes necrotic, and retinal detachment with multiple ragged retinal holes occurs in about three-quarters of severe cases 4–8 weeks after the onset of retinitis [10]. Recurrences are rare in the immunocompetent patient.

The distinctive and particularly virulent RPHRN variant of herpetic retinitis is a much more frequent manifestation of herpetic infection in patients with advanced HIV disease than is
Materials and Methods

We studied 11 patients with the RPHRN syndrome. All patients fulfilled current criteria of the Centers for Disease Control and Prevention for the diagnosis of AIDS [21]. The ophthalmological and internal medicine charts, both inpatient and outpatient, were reviewed retrospectively. The following information was collated: age; sex; HIV risk factors; CD4 cell counts; history of previous VZV, HSV, or CMV disease; time of onset of ocular symptoms; extent and type of involvement; treatment regimens; associated findings; and disease progression. All but three patients had been under the care of the Division of Infectious and Tropical Disease at the University of South Florida (Tampa). Two eyes (cases 1 and 2) were studied by conventional ocular histopathology and electron microscopy, and tissue was analyzed for VZV DNA by PCR analysis (performed by Dr. Beverley Connelly at Children’s Hospital Medical Center, Cincinnati, OH) [22]. The other patients’ eyes were not investigated. One patient (number 2) has been described briefly in a print publication [23], and two (patients 7 and 8) have been reported on the Internet [24].

Results

An outline of the presentation, management, and outcomes of the 11 cases is shown in table 1. The 11 patients comprised 7 men and 4 women. Ages ranged from 27 to 40 years. No association of RPHRN with HIV risk factors was apparent, as four homosexuals, two heterosexuals, three intravenous drug users, and a hemophiliac were represented; one patient had no known risk factor. The mean CD4 cell count was 24/μL, with a range of 5–83 cells/μL. Cutaneous zoster preceded the clinical onset of RPHRN in eight patients (73%) by 3 weeks to 20 months (recurrent zoster in 2 patients); only 1 case had involved a trigeminal nerve.

Zosteriform rashes were conspicuously absent in all cases during the course of the viral retinitis. Two patients had concurrent culture-proven HSV infections, one patient had inactive HSV infection, and the status of the cutaneous cold sores in a fourth patient was not recorded. There was clinical evidence to suggest an HSV etiology of the RPHRN in one patient (case 3—see below).

A total of 20 eyes with RPHRN were evaluated. Bilateral retinal involvement occurred in nine of 11 patients (82%). The disease presented bilaterally in six patients (55%) but rapidly involved the second eye in another three patients. Two patients with unilateral disease at presentation (patients 5 and 7) avoided second-eye involvement over 10 and 13 months, respectively; patient 5 refused all antiviral therapy for the last 7 months of life.

At presentation, the visual acuity of involved eyes varied from 20/20 to no light perception. Six eyes had visual acuities in the range of 20/20 to 20/50; six eyes had acuities of 20/60 to 20/200; and eight eyes had visual acuities of count fingers, hand movements, light perception, or no light perception. Fourteen of the 20 eyes (70%) developed retinal detachments, which were usually extensive; these were noted at first presentation in four eyes and developed at 2–6 weeks in the remainder.

At last follow-up, despite intensive inpatient and maintenance antiviral therapy, as well as vitrectomy surgeries with internal silicone oil tamponade for retinal detachments (undertaken in eyes with visual potential), the best corrected visual acuities (for the 20 eyes) were reduced to 20/60 in 2 eyes, 20/80 in 1 eye, 20/150 in 1 eye (with 2 months’ survival), counting fingers in 2 eyes, and no light perception in 14 eyes (70%). Most visual loss was rapidly progressive in spite of treatment. Two eyes (patients 2 and 11) progressively lost vision over the first 2 months. In two eyes (patients 4 and 5), final visual failure was delayed for 6 months and was apparently caused by superimposed viral optic neuritis, without evidence of retinal recurrence. The demographic data are summarized in table 2.

The involved eyes had a uniform appearance. Extensive areas of one or both retinas showed outer retinal opacification with considerable multifocality, smaller satellite lesions, and progression within a few days to confluence. The retinal vessels did not appear to be involved primarily, and clinical intraocular inflammation was absent or mild. Moderate preretinal hemorrhage occurred in a minority. Progression was rapid, with early foveal involvement. Early clearing of perivascular lacunae ensued. These changes are illustrated in figures 1A–C.

Ocular histopathology was performed on patients 1 and 2 (figures 2, 3A, and 3B). These cases illustrate the early and late pathological findings. VZV DNA was demonstrated in optic nerve tissue in patient 1 and in retina in patient 2 by means of a PCR-based detection system [22]. Retinal detachments with large, multiple, irregular, atrophic retinal tears occurred in the majority of eyes, with a median onset of 2 weeks after presentation.

Case Reports

Case 1 (Patient 3)

A 31-year-old Ethiopian woman presented in October 1990 with a 3-year history of HIV infection complicated by tuberculous enteritis, oropharyngeal candidiasis, oral hairy leukoplakia, recurrent perioral HSV infections, molluscum contagioso-
Table 1. Clinical features and outcomes for 11 patients with AIDS-associated rapidly progressive herpetic retinal necrosis (RPHRN).

<table>
<thead>
<tr>
<th>Patient no.: age (y)/sex</th>
<th>No. of CD4 cells/μL</th>
<th>Initial VA*</th>
<th>Viral infection before onset</th>
<th>Other AIDS-related disease</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
<td>Varicella-zoster</td>
<td>Herpes simplex</td>
<td></td>
</tr>
<tr>
<td>1: 36/M</td>
<td>10</td>
<td>CF</td>
<td>CF</td>
<td>...</td>
<td>11</td>
</tr>
<tr>
<td>2: 39/M†</td>
<td>14</td>
<td>20/20</td>
<td>20/25</td>
<td>17 mo</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: 31/F</td>
<td>51</td>
<td>LP</td>
<td>20/25</td>
<td>Recurrent (oral)</td>
<td></td>
</tr>
<tr>
<td>4: 28/M</td>
<td>5</td>
<td>20/200</td>
<td>CF</td>
<td>4 mo</td>
<td></td>
</tr>
<tr>
<td>5: 38/M</td>
<td>10</td>
<td>(20/20)</td>
<td>20/20</td>
<td>Recurrent (genital)</td>
<td></td>
</tr>
<tr>
<td>6: 29/F</td>
<td>12</td>
<td>20/100</td>
<td>20/100</td>
<td>24 mo</td>
<td></td>
</tr>
<tr>
<td>7: 35/M</td>
<td>50</td>
<td>(20/25)</td>
<td>20/70</td>
<td>Prior esophagitis</td>
<td></td>
</tr>
<tr>
<td>8: 37/F</td>
<td>10</td>
<td>20/30</td>
<td>20/60</td>
<td>3 w</td>
<td></td>
</tr>
<tr>
<td>9: 27/M</td>
<td>83</td>
<td>20/70</td>
<td>CF</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td>10: 40/M</td>
<td>10</td>
<td>20/70</td>
<td>20/400</td>
<td>26 mo</td>
<td></td>
</tr>
<tr>
<td>11: 39/F</td>
<td>8</td>
<td>CF</td>
<td>NLP</td>
<td>4 mo</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. ACV = acyclovir; CF = count fingers; CMV = cytomegalovirus; FOS = foscarnet; GCV = ganciclovir; IVIT = intravitreal; LP = light perception; NLP = no light perception; OD = right eye; OS = left eye; OU = both eyes; TB = tuberculosis; VA = Snellen visual acuity.

* The visual acuities in parentheses are for uninvolved eyes.

† Reported previously [23].
§ Peripheral retinal detachments successfully controlled with laser photoagulation.

sum, and two episodes of Pneumocystis carinii pneumonia. She had never had shingles. Her CD4 cell count was 51/μL. There had been rapid visual loss OD (oculus dexter: right eye) over several days, with visual acuities of light perception OD and 20/25 OS (oculus sinister: left eye), coincidental with the onset of bilateral partial 6th cranial nerve palsies. The right eye showed massive outer retinal opacification with partial sparing of the macula (figure 4). The left eye showed a classical granular CMV lesion in the temporal retinal periphery, without evidence of RPHRN. Despite induction with intravenous ganciclovir (Cytovene [5 mg/kg twice daily]; Syntex, Palo Alto, CA), the right retina detached and extensive RPHRN OS developed rapidly.

Intravenous foscarnet (Foscavir; Astra, Westborough, MA), at a dosage of 90 mg/(kg·d) three times daily, and twice-weekly injections of intraocular ganciclovir (200 μg/0.1 mL) OS were instituted, but the RPHRN OS progressed rapidly and the patient developed a total retinal detachment. Scleral buckle surgery with pars plana vitrectomy and silicone oil internal tamponade finally attached the retina, but no-light-perception
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Change in treatment</th>
<th>Outcome</th>
<th>Retinal detachment</th>
<th>Final VA*</th>
<th>CNS involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV GCV</td>
<td>IV FOS</td>
<td>Rapid progression</td>
<td>OS</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>IV GCV</td>
<td>IV FOS</td>
<td>Rapid progression</td>
<td>OU decreased over 2 mo</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>IV ACV, IV GCV</td>
<td>IVIT GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>Oral ACV, IV GCV</td>
<td>IV ACV, oral GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>Oral ACV, IV GCV</td>
<td>IV ACV, oral GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>Oral ACV, IV GCV</td>
<td>IV ACV, IV FOS, IVIT GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>Oral ACV, IV GCV</td>
<td>IV ACV, IV FOS, IVIT GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
<tr>
<td>Oral ACV, IV GCV</td>
<td>IV ACV, IV FOS, IVIT GCV</td>
<td>Rapid progression</td>
<td>OU</td>
<td>NLP</td>
<td>NLP</td>
</tr>
</tbody>
</table>

vision OU (oculi unitis: both eyes) rapidly intervened. One month later, she became unresponsive to verbal stimuli owing to undiagnosed encephalitis; serial brain CTs and MRIs were normal. Examination of CSF showed a raised protein level of 75 mg/mL. She failed to respond to intravenous ganciclovir and died 2 months later after seizures developed.

**Case 2 (Patient 5)**

A 38-year-old Puerto Rican former intravenous drug user was found in 1992 to have HIV infection. He had been treated subsequently for oropharyngeal candidiasis, hepatic tuberculosis, recurrent HSV genital infection, hepatitis C infection, and an episode of *P. carinii* pneumonia in August 1993. Lumbar dermatomal zoster had been diagnosed in April 1993. His CD4 cell count was 10/μL.

In December 1994, coincident with a culture-positive recurrence of genital HSV infection, he presented with a 2-week history of progressive tunnel vision in his left eye, with mild photophobia and retro-orbital pain. His visual acuity was 20/20 OU. The right eye was normal. The left eye showed
Table 2. Summary of demographic and clinical data regarding patients with rapidly progressive herpetic retinal necrosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes involved</td>
<td>20 (91)</td>
</tr>
<tr>
<td>Age; mean; median (y)</td>
<td>34; 36</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (36)</td>
</tr>
<tr>
<td>HIV risk factor</td>
<td></td>
</tr>
<tr>
<td>Homosexuality</td>
<td>4</td>
</tr>
<tr>
<td>Heterosexuality</td>
<td>2</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>3</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>No. of CD4 cells per μL; range; median</td>
<td>5–85; 12</td>
</tr>
<tr>
<td>Prior VZV infection</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Prior recurrent HSV infection</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Concurrent CMV retinitis (n = 20)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Presenting symptom(s) in worse eye</td>
<td></td>
</tr>
<tr>
<td>Blurring: central visual loss</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Peripheral/paracentral visual field loss</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Flashes and floaters</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Retinal detachment in involved eyes (n = 20)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Onset (median, 2 w after presentation)</td>
<td></td>
</tr>
<tr>
<td>At presentation</td>
<td>4</td>
</tr>
<tr>
<td>≤2 w</td>
<td>1</td>
</tr>
<tr>
<td>2–6 w</td>
<td>9</td>
</tr>
</tbody>
</table>

NOTE. CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella-zoster virus.

characteristic confluent outer retinal whitening involving the entire retinal periphery and mid-periphery, with a few small, scattered areas of involvement in the extrafoveal macula. Perivascular clearing (lacunae) rapidly developed (figure 5). The optic nerve was normal. There were almost no intraocular inflammatory signs, but episcleritis was present OS.

The patient was treated with oral acyclovir (Zovirax; Burroughs-Wellcome, Research Triangle Park, NC) at a dosage of 800 mg q.i.d. and intravenous ganciclovir (5 mg/[kg · d]) for 2 months, but he declined further intravenous and oral treatment. After the first 3 weeks of treatment, multiple irregular retinal holes developed in the involved inferonasal retina OS with a segmental, “macula-on” retinal detachment. Pars plana vitrectomy and silicone oil injection successfully flattened the retina.

His vision stabilized for 6 months at 20/40 OS with a contact lens, but progressive visual loss ensued over the next 4 weeks to no light perception, in the absence of clinical evidence of retinal recurrence. Simultaneously, he was being treated with external irradiation (total, 4,000 cGy) for newly diagnosed left antral lymphoma. The optic nerve became pale and had presumably been damaged by recurrent herpetic optic neuritis because of the rapidity of onset and progression, rather than by radiation-induced optic neuropathy, the effect of which would be delayed.

Figure 1. Rapidly progressive herpetic necrotizing retinitis (RPHNR) in patient 9. A, right eye: multifocal outer retinal opacification involving entire inferior retina, with early macular involvement (not shown). Visual acuity, 20/70. B, left eye: focus of classical RPHNR central macular involvement. The retinal opacification has begun to recede from the foveal center, leaving a lacuna of atrophic retina in its place. Visual acuity, counting fingers. (The camera is misaligned.) C, nasal retina: most of the extramacular retina involved with confluent retinitis. Note preretinal hemorrhage and early development of lacunae within involved retina.
Although the patient declined to take antiviral therapy, the right eye remained uninvolved until he succumbed to recurrent P. carinii pneumonia in September 1995. The patient had no neurological symptoms and there was no clinical evidence of herpesvirus dissemination; two brain CTs were negative.

Case 3 (Patient 6)

A 29-year-old former intravenous drug user had HIV infection that had been diagnosed 6 years previously. She had been treated for P. carinii pneumonia in 1989; severe, chronic wasting disease; left dorsal dermatomal zoster in March 1993; Mycobacterium avium infection (since March 1994); and bilateral CMV retinitis (since April 1994). The CMV retinitis was treated initially with intravenous ganciclovir but then with foscarnet when it progressed. Her visual acuities were maintained at 20/30 OU. For >1 year there had been a stationary, segmental iris atrophy OD of a type characteristic of VZV uveitis, but with only minimal uveitis and no evidence of prior herpes zoster ophthalmicus.

In March 1995 a few small, subtle, white featherly retinal infiltrates were noticed in the far temporal retinal periphery OS. There were no inflammatory signs or evidence of CMV retinitis activity. The patient failed to return when requested. Two weeks later, she noticed a rapid visual loss in both eyes. She had become unwell and nauseated and had taken no foscarnet for 2 weeks. Her visual acuities were 20/100 OU. There was a concurrent culture-positive HSV genital infection, and the left iris showed for the first time an oval mid-iris atrophy at 10 o’clock, with an appearance characteristic of HSV infection [25].

Both eyes had developed RPHRN with a somewhat atypical appearance. The retinal opacification was diffusely gray and opalescent (figure 6), in contrast to the distinct outer retinal whitening characteristic of RPHRN. There were few inflammatory signs, and retinal vasculitis was absent. In the left eye there was panretinal involvement of all areas except those scarred by old CMV retinitis, and a retinal detachment was present; no-light-perception vision developed rapidly OS. The right eye had involvement of the superior 40% of the retina, with a few small, round lesions in the extrafoveal macula.

She was treated with intravenous acyclovir (15 mg/(kg · d)) and foscarnet (120 mg/(kg · d)). Alternating three-times-a-week intravitreal injections of ganciclovir (2,000 μg) and foscarnet (2,400 μg) were given over the first month, at which time a macula-on retinal detachment developed OD, involving the superior retina and extending close to the foveal center. She underwent a pars plana vitrectomy and silicone oil injection, followed by alternating thrice-weekly intravitreal injections OD at lower dosages (ganciclovir, 1,000 μg; foscarnet, 1,200 μg).

The viral retinitis became quiescent OD, with a visual acuity of 20/150. She died 2 months after the development of RPHRN.
Figure 4. Case 1 (patient 3): severe RPHRN OD, with presumed optic nerve involvement (visual acuity: light perception). Within 3 weeks, the patient lost light perception in both eyes.

Although there were two prolonged episodes of confusion over the last 3 months of her life, brain MRI with contrast showed only diffuse cerebral atrophy. There was no other clinical evidence of disseminated herpetic disease.

Case 4 (Patient 7)

A 35-year-old man with a 2-year history of HIV infection and a CD4 cell count of 50/µL presented in July 1995 because of a 2-week history of blurred vision in his left eye. His visual acuities were 20/25 OD and 20/70 OS. There was no history of previous VZV infection, although he had been treated for HSV esophagitis 6 months previously. The right eye was normal. There were modest inflammatory signs OS with circumferential, outer retinal opacification of the entire retinal periphery OS, isolated foci involving the fovea and temporal macula, and an absence of retinal vasculitis.

His RPHRN OS was treated with a combination of oral acyclovir (800 mg every 4 hours) and alternating two-to-three-times-weekly intravitreal injections OS of ganciclovir (2,800 µg/0.1 mL) and foscarnet (2,400 µg/0.1 mL). One week after the initiation of this therapy, there was partial regression of the retinal opacification OS, and almost complete resolution occurred by 1 month. The treatment regimen was continued.

The visual acuity stabilized at 20/100 OS before an extensive extrafoveal retinal detachment developed, necessitating pars plana vitrectomy, endolaser treatment, and silicone-oil injection OS. The retina was reattached. Maintenance therapy was established with oral acyclovir (800 mg po b.i.d.) and alternating intravitreal injections of ganciclovir (1,000 µg) and foscarnet (1,200 µg), given initially twice weekly and later at 2-week intervals. The visual acuity stabilized at 20/80 OS, without recurrence of disease.

The patient required a cataract extraction with an intraocular lens OS after 8 months. There was no involvement of the second eye during treatment with acyclovir (800 mg twice daily). He remained well at 13 months, without evidence of CNS disease. The CD4 cell count increased to 200/µL with administration of saquinavir (Invirase; Roche, Nutley, NJ), started after stabilization of the RPHRN.

Figure 5. Case 2 (patient 5): confluent outer retinal opacification OS from RPHRN, with perivascular clearing (lacunae); visual acuity: 20/40. No-light-perception vision and retinal detachment rapidly ensued.

Figure 6. Case 3 (patient 6): atypical milky opacification of retina OS diffusely involved with RPHRN, believed to be caused by HSV (per clinical evidence). Visual acuity: 20/100. The inferior retinal periphery is scarred by old CMV retinitis (asterisk) and delimits the area of retinal necrosis (arrows). No-light-perception vision and retinal detachment rapidly ensued.

Case 5 (Patient 8)

A 37-year-old woman known to have HIV infection since 1989 presented in December 1995 because of several days of visual loss in the left eye. The CD4 cell count was 10/µL. Her
visual acuity was 20/30 OD and 20/60 OS, with an afferent pupillary defect OS. There had been an episode of right thoracolumbar multidermatomal zoster 3 weeks earlier that had resolved without antiviral treatment. Slit-lamp examination showed a mild anterior uveitis OS. Indirect ophthalmoscopy yielded bilateral findings of both RPHRN and undiagnosed, classic CMV retinitis. There were small, multifocal RPHRN lesions in the far inferotemporal periphery OD, without foveal involvement. Examination of the left eye showed large multifocal lesions in the superior retinal periphery OS; optic nerve involvement was surmised to be the cause of visual loss. Early peripheral CMV retinitis of granular appearance was present OD, with a large area of typical CMV disease in the inferior periphery OS.

Treatment was initiated with oral acyclovir (800 mg five times daily) and bilateral, alternating intravitreal injections of ganciclovir (increasing from 2,000 μg to 3,600 μg/0.1 mL and foscarnet (increasing from 2,400 μg/0.1 mL to 4,800 μg/0.2 mL) given every other day. There was rapid disease extension in both eyes. The visual acuity OS fell to count-fingers vision after 2 days because of optic nerve involvement.

Despite continuing intensive treatment, new lesions continued to appear and expand OD over the first 7 days. Oral acyclovir was increased to 1,600 mg five times daily. Multiple cotton-wool spots (nerve fiber layer infarcts) appeared in the right retina between days 7 and 16. Although the cotton wool spots were unilateral and likely to be caused by HIV microangiopathy, the possibility of drug toxicity could not be excluded, so the intravitreal injections were discontinued and replaced with administration of intravenous foscarnet (60 mg/kg twice daily) and intravenous acyclovir (15 mg/kg every 8 hours).

After 30 days the patient stabilized, with remission of disease activity. Bilateral peripheral retinal detachments were localized successfully with laser treatment. The CMV retinitis became quiescent. Visual acuities were stabilized at 20/60 OD and count-fingers vision OS at 8 months, with no recurrence of the viral retinitis on a maintenance regimen of intravenous acyclovir (400 mg/d twice daily) and foscarnet (2.4 g daily).

Six weeks following the initiation of RPHRN antiviral therapy, the patient was admitted because of a *Staphylococcus aureus* septic thrombophlebitis of the left subclavian vein, complicated by the development of multiple intracranial mycotic aneurysms. Bilateral demyelinating lesions were detected in the occipital lobe white matter and corpus callosum on T1 MRI in association with a severe encephalopathic picture that gradually settled, with marked improvement of the neuroimaging findings. She remained remarkably well after 11 months.

**Discussion**

RPHRN, a newly characterized disease syndrome that has become a relatively frequent accompaniment of advanced HIV infection [2–4, 9, 20], is the second most common AIDS-associated opportunistic retinal infection in the United States after CMV retinitis [26]. Distinctive features of RPHRN include the appearance of outer retinal opacification, a general absence of significant inflammatory signs in the eye, bilaterality, and multifocality. The rapid progression to confluence; early involvement of the fovea and/or optic nerve; lack of the chronic “granular” retinal infiltration and retinal hemorrhages typical of CMV retinitis; rapid clearance of the outer retinal opacification over 1–2 weeks with the development of lacunae in the early evolution of the retinitis [15]; and very high rates of precipitate, bilateral total blindness are other important diagnostic features [4, 9, 15–17, 26, 27]. In at least 65%–70% of eyes, RPHRN leads to early retinal detachments, which are associated with multiple ragged retinal tears, often posteriorly located [4, 9, 27].

This disease has also been known as progressive outer retinal necrosis (PORN) because of a misconception that the appearance of outer retinal opacification represents outer retinal zonal necrosis. As the histopathologic investigations in two cases in this study emphasize, the retinal necrosis involves the entire thickness of the neurosensory retina as well as the retinal pigment epithelium. Indeed, the retina in case 2 showed more extensive involvement of the inner retinal layers. We and others therefore choose to avoid using the PORN nomenclature [28–30], preferring instead the designation RPHRN. Despite severe retinal necrosis, there are almost no inflammatory cells present, except for macrophages during tissue remodeling. The characteristic perivenular clearing and rapid evolution of lacunae are due to the scavenging of retinal necrosis and provide a clinical correlate of the noninflammatory and noninfiltrative nature of the retinal opacification.

ARN and RPHRN represent the polar opposites of a viral retinitis spectrum, reflecting degrees of immunosuppression and/or differences in viral strain virulence. Some cases do not fit the clinical criteria for either of these two diseases; one such case has been described by Jabs and colleagues [12].

Until recently, VZV has been the only etiologic agent confirmed to cause RPHRN. We isolated VZV genomic material from optic nerve tissue in case 1 (there was no surviving retinal tissue available) and from retinal tissue in case 2 (patient 5); the other cases were not tested. Herpesvirus particles can usually be detected by electron microscopy in such cases as long as enough retinal tissue survives in the specimen [2, 11, 15]. VZV has been detected by viral isolation [15, 27], immunohistochemistry [15, 27], and PCR amplification [30–33]. Evidence of local intraocular specific-antibody production may also be helpful [34]. All but three patients reported previous episodes of shingles at a median prior interval of 6 months (range, 3 weeks to 24 months).

Diagnostic PCR assays have recently implicated HSV-1 and HSV-2 as occasional causes of RPHRN [35]. Indeed, there was clinical evidence in patient 6 (case 3) in our series that suggested HSV as the etiologic agent. This patient had shingles 24 months before presentation and subsequently developed a classical zoster-associated segmental iris atrophy OD in the absence of herpes zoster ophthalmicus. The later development
of RPHRN was concomitant with recrudescence of culture-positive HSV dermatitis and also coincided with the development of an oval mid-iris atrophy in the opposite eye, characteristic of HSV uveitis [25].

The bilateral retinal opacification in this case was opalescent rather than opaque, perhaps also indicative of an HSV etiology, but the retinitis otherwise behaved typically of RPHRN. A VZV etiology could not be excluded. Atypical cases of HSV retinitis in immunocompetent individuals have also been described [36].

This series confirms the appalling visual outlook of rapidly progressive herpetic necrotizing retinitis with the present therapy. Only four of 20 involved eyes in this series retained useful vision, with acuities of 20/60 (two patients), 20/80, and 20/150 after 6, 11, 13, and 2 months of follow-up, respectively. Fourteen eyes (70%) had no light perception, and two eyes had counting-fingers visual acuity at the termination of the study.

Engstrom and colleagues reported that two-thirds of 63 eyes progressed to no-light-perception visual acuity within 1 month of diagnosis, despite intensive intravenous antiviral therapy [27]. Moorjhy et al. [29] recorded that half of 39 eyes had no-light-perception vision within a median follow-up period of 6 months. Our data further emphasize that loss of vision from RPHRN is usually not a preterminal event, as the mean survival from diagnosis was 9.5 months (range, 2 to 22+ months), with five of 11 patients still living.

In many eyes with initially scattered lesions, disease continued to progress, with coalescence and enlargement of lesions and involvement of the fovea and optic nerve, despite apparently adequate antiviral therapy. In two patients, late visual failure was believed to be caused by recurrent viral optic neuritis in the absence of overt active retinitis. CMV retinitis preceded RPHRN in two patients (three eyes). In one eye, the RPHRN retinitis involved all remaining retina, which was outlined by the atrophic CMV retinitis scarring.

Many aspects of RPHRN pathogenesis are not understood. Remote cutaneous zoster generally occurred in these patients several months previously. This temporal association suggests the likelihood of hematogenous dissemination during the initial zoster eruption [37]. The high frequency of bilateral, simultaneous retinal involvement in patients with RPHRN and the rapidity of the disease process are consistent with spread along nerve pathways within the anterior visual system. Intraneuronal [38] and transsynaptic [39] propagation of VZV has been well documented. In patient 1, we demonstrated for the first time in RPHRN cytopathic and PCR evidence of direct VZV invasion of the optic nerve. Recently, VZV was isolated from the CSF of a patient with AIDS who presented with bilateral optic neuritis and subsequently developed bilateral RPHRN [39].

The possible role of the relative immune privilege of the eye [41] must also be considered. The absence of contemporaneous cutaneous shingles and general lack of visceral varicella involvement in patients with RPHRN [4, 9, 15, 27] support the hypothesis that RPHRN is a local VZV recurrence with local ocular and neural dissemination. These factors also suggest that persisting or intermittent viremia is unlikely to be a common etiologic factor.

Rousseau and colleagues [42] have recently drawn attention to VZV CNS involvement in patients with RPHRN. They described three patients with symptomatic CNS disease and neuroradiological evidence of cerebral vasculitis. Three additional cases of VZV antigen–positive encephalitis, closely associated with the onset of RPHRN, and cases with VZV cerebral vasculitis and meningitis are now described [28, 29, 43]. A comprehensive review of the medical charts of our 11 patients revealed eight (73%) with CNS disease that may have been VZV-related, varying from unexplained confusional episodes to focal brain syndromes to severe encephalopathic disease. Patients generally responded to the intensive antiviral therapies employed (table 1), with cessation of symptoms and signs. Postmortem studies were not performed.

VZV infection of the CNS in patients with AIDS [44] may not be as rare as previously believed [45]. Several patterns of CNS VZV involvement complicating AIDS have been described, including encephalitis without cutaneous eruption [45, 46], brain stem demyelination with multiple cranial nerve palsies [47], myelitis accompanying zoster dermatitis [45, 48, 49], meningoymeloradiculitis caused by necrotizing CNS vasculitis [45, 50], and leptomenigitis causing stroke [45]. VZV encephalitis has typically been described as occurring within 2 or 3 weeks of cutaneous zoster, with a rapid onset of CNS symptoms and the occurrence of multifocal necrotic or demyelinating lesions that predominate in the white matter, the white-grey matter junction, or periventricular areas [45, 51].

The question of how frequently the CNS and viscera are involved in RPHRN must be evaluated prospectively. It seems unlikely that VZV would solely involve the eyes in all such cases. Autopsy studies of patients with RPHRN are also needed to help define the systemic disease implications if protocols are to be devised to prevent its occurrence and optimize its treatment.

AIDS-associated RPHRN has proved almost impossible to treat satisfactorily with conventional antiviral regimens. Engstrom et al. [27] described the results of treatment in 38 patients (65 involved eyes) and concluded that intensive antiviral treatment with acyclovir did not appear to affect final visual outcome and did not prevent involvement of the second eye. Visual acuity was reduced to no light perception in two-thirds of eyes within 1 month of diagnosis [27]. Quiescence of the viral retinitis could be achieved in only 18% of patients with high-dose intravenous acyclovir (>10 mg/kg every 8 hours), and recurrence of disease was often temporally associated with reduction of acyclovir dosage to a maintenance schedule [27]. Their findings are mirrored by other published cases [2, 11, 13–16, 18, 19, 27, 29, 31–33, 52, 53].

Only four of 20 involved eyes in this series retained useful vision with an average follow-up of 9.5 months. The varied therapeutic approaches used and the clinical responses achieved
are summarized in table 1. Single intravenous ganciclovir therapy was associated with rapid disease progression in three patients. Initial high-dose combination therapy was used in 8 patients and included the use of oral acyclovir in 3 patients, intravenous acyclovir in 5, intravenous ganciclovir in 3, intravenous foscarnet in 5, repeated intravitreal ganciclovir injections in 4, and repeated intravitreal foscarnet injections in 5. Drug toxicity was not reported in this study.

The therapeutic response was quite variable, and it is not yet possible to make definitive therapeutic recommendations. The rationale for using ganciclovir was derived partly from the results of the SOCA (Studies of Ocular Complications of AIDS) Research Group in the treatment of CMV retinitis with both ganciclovir and foscarnet [54]. Clinical studies in RPHRN have also suggested improved results with the use of ganciclovir and foscarnet [28, 29, 33, 53]. Repeated intravitreal injections of foscarnet and ganciclovir along with oral acyclovir (2 patients) and combinations of intravenous acyclovir with either ganciclovir (1 patient) or foscarnet (1 patient) were the treatment regimens utilized in the patients with affected eyes (patients 6–9: 4 eyes) that retained useful vision.

The limited ocular bioavailability of oral and systemic antivirals suggests that intensive local ocular therapy with the repeated high-dose intracocular injection of antivirals and combination intravenous therapy may be the most logical available treatment at present, especially given the poor results for most patients treated with parenteral antiviral therapy alone. This is provisional advocacy, as clearly there is an urgent need for formal therapeutic investigations. The potential effect of the protease inhibitors on altering the natural history of RPHRN by modulating AIDS immunosuppression also awaits future study; they were available to only one patient in this report (patient 7).

The cumulative experience in the management of RPHRN contrasts with the usually satisfactory response to treatment achieved in the ARN syndrome caused by VZV in immuno-compotent individuals. Intravenous acyclovir (10 mg/kg every 8 hours for 10–14 days), followed by oral acyclovir (400 mg five times daily for 4–6 weeks), is usually successful at controlling ARN [10, 55, 56]. A similar dosage regimen, adjusted for impaired renal function, is recommended also for HIV-infected patients with visceral or disseminated zoster.

The reasons for the failure of intravenous acyclovir in RPHRN must be elucidated. Ocular histopathological investigations are needed to investigate whether the VZV is perhaps widely distributed throughout the normal-appearing retina at presentation, implying that severe retinal damage might be predetermined at diagnosis. The propensity for recurrence of disease at the margins of previous retinal lesions [27] suggests that this may not be the case. Intraocular antiviral levels must also be studied, as the occlusive vasculopathy causes poor retinal perfusion in RPHRN [57] and may impair the access of systemic antivirals to the eye. Retinal tissues are already relatively isolated behind blood-ocular barriers.

Virus isolation from the eye is important if the roles of antiviral resistance and of strain differences are to be investigated. Most patients with RPHRN have received oral acyclovir previously in the management of AIDS-associated cutaneous zoster or recurrent HSV infections. Indeed, acyclovir resistance is known to be a relatively common occurrence in the course of repeated or prolonged VZV infections in patients with AIDS [58, 59]. Resistance of VZV to acyclovir is caused by nucleotide deletions or amino acid substitutions within VZV thymidine kinase genes that result in diminished activity of the enzyme and impaired activity of thymidine kinase–dependent antivirals [60]. The long-term use of oral and intravenous ganciclovir to prevent or treat concomitant CMV infection is also common in these patients. Acyclovir resistance uniformly results in cross-resistance to ganciclovir, as both drugs require activation by viral thymidine kinase [60].

Viral resistance has been demonstrated in a case of RPHRN [61]. If acyclovir and ganciclovir resistance is a common cause of treatment failure in RPHRN, foscarinet is the logical primary therapy. Foscarinet has activity against both VZV and HSV, directly inhibits viral DNA polymerase, and is not dependent on viral thymidine kinase for its antiviral effect. It has also been shown to be effective in the management of acyclovir-resistant VZV [59, 62] and HSV [63, 64] infections. Limited experience with intravenous foscarinet (60–90 mg/kg 3 times daily) in combination with acyclovir or ganciclovir has been reported on with regard to several cases of RPHRN; it was used with some success [65] but also with significant failures. It is obvious that more effective treatment regimens are required.

The utility of antiviral agents with increased bioavailability, such as famciclovir (Famvir; SmithKline Beecham, Pittsburgh) or valacyclovir (Valtrex; Eurroughs-Wellcome, Research Triangle Park, NC), or with enhanced antiviral activity, such as sorivudine (Bristol Myers Squibb, Princeton, NJ) or HPMPC (Cidofovir; Gilead, Foster City, CA), [50] deserves exploration. However, famciclovir, valacyclovir, and sorivudine all require viral thymidine kinase for activation, so cross-resistance with acyclovir might be anticipated. Maintenance antiviral protocols are a major problem. Too often, the use of reduced antiviral levels in maintenance therapy is associated with the onset of rapid deterioration and severe visual loss.

The extremely poor visual prognosis and problematic management for patients who develop RPHRN deserve greater recognition. This series emphasizes the seminal features of this newly described and devastating viral necrotizing retinopathy that has arisen as a complication of late-stage AIDS. The rapid and often bilateral total visual loss in these patients reflects our current failure to control viral proliferation and our inability to avert the sequelae of retinal necrosis. The possible prophylactic role of early aggressive intravenous acyclovir therapy in AIDS-associated shingles to prevent viral dissemination to the eye and elsewhere needs to be explored.

Our experience speaks urgently to the necessity of collaborative research between infectious disease specialists, virologists, immunologists, and vitreoretinal specialists to understand the disease process adequately and to develop successful therapy and prophylaxis for this condition.
References


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