

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 $24/\mu\text{L}$. 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 immunoprivileged 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.

See editorial response by Lowder on pages 46-7.

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

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ARN [11–20]. Predominantly confined to patients with AIDS, RPHRN causes a fulminant and almost always bilateral retinitis, characterized by rapidly progressive multifocal lesions with the appearance of outer retinal opacification, often early macular involvement, minimal inflammatory signs, a poor response to conventional intravenous antiviral medication, and complex bilateral retinal detachments in the majority—the sum of which usually results in total blindness. This article is written to draw attention to this devastating condition and to highlight the urgent need for collaborative research into improving its treatment and prevention.

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/ μ L, with a range of 5–83 cells/ μ L. 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 contagio-

Table 1. Clinical features and outcomes for 11 patients with AIDS-associated rapidly progressive herpetic retinal necrosis (RPHRN).

Patient no: age (y)/sex	No. of CD4 cells/ μ L	Initial VA*			Viral infection before onset			Other AIDS-related disease	Survival (mo)
		OD	OS	VA	Varicella-zoster	Herpes simplex	VA		
1: 36/M	10	CF	CF	Pneumocystic pneumonia, CMV esophagitis, wasting, [†] oral candidiasis (Index presentation)	11	
2: 39/M [‡]	14	20/20	20/25	17 mo 6 mo		21	
3: 31/F	51	LP	20/25	...	Recurrent (oral)	...	TB enteritis, pneumocystic pneumonia, oral candidiasis	2	
4: 28/M	5	20/200	CF	4 mo	Pneumocystic pneumonia	22+	
5: 38/M	10	(20/20)	20/20	20 mo	Recurrent (genital)	...	Pneumocystic pneumonia, oral candidiasis, hepatic TB, hepatitis C	10	
6: 29/F	12	20/100	20/100	24 mo	Recurrent (genital)	...	Pneumocystic pneumonia, <i>Mycobacterium avium</i> infection, CMV retinitis, wasting	2	
7: 35/M	50	(20/25)	20/70	...	Prior esophagitis	...	Pneumocystic pneumonia	13+	
8: 37/F	10	20/30	20/60	3 w	CMV retinitis, wasting	11+	
9: 27/M	83	20/70	CF	6 mo	Stroke—old right hemiplegia	6+	
10: 40/M	10	20/70	20/400	26 mo 6 mo	<i>M. avium</i> infection, cryptococcal meningitis and dissemination, Kaposi's sarcoma (Index presentation)	2	
11: 39/F	8	CF	NLP	4 mo		4+	

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 photocoagulation.

sum, and two episodes of *Pneumocystis carinii* pneumonia. She had never had shingles. Her CD4 cell count was 51/ μ L. 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 gan-

ciclovir (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 μ g/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)

Therapy	Change in treatment	Outcome	Retinal detachment	Final VA*		
				OD	OS	CNS involvement
IV GCV	IV FOS	Rapid progression	OS	NLP	NLP	Dysphasic episode, unexplained seizures
IV GCV	IV FOS	Rapid progression	...	NLP	NLP	Unexplained seizures
IV ACV	IV ACV	OU decreased over 2 mo	...	NLP	NLP	CT negative
IV GCV, IV FOS	IVIT GCV	Rapid progression	OU	NLP	NLP	Bilateral 6th cranial nerve palsies, encephalitis, seizures
IV ACV, IV GCV	IV ACV, oral GCV	Rapid progression	OU	NLP	NLP	...
Oral ACV, IV GCV	Noncompliant; oral ACV, oral GCV	OD remained uninvolved; OS stable for 6 mo, then VA declined	OS	(20/20)	NLP	...
IV ACV, IV FOS, IVIT GCV, IVIT FOS	...	Progressed initially; stabilized in 1 mo	OU	20/150	NLP	Episodes of confusion, cerebral atrophy (MRI)
Oral ACV, IVIT GCV, IVIT FOS	...	OD remained uninvolved; OS stabilized in 1 w	OS	(20/25)	20/80	...
Oral ACV, IVIT GCV, IVIT FOS	IV ACV, IV FOS, IVIT GCV, IVIT FOS	Rapid progression	OU [†]	20/60	CF	Intracranial mycotic aneurysms, reversible encephalopathy, abnormal T ₂ signal (MRI) in corpus callosum and occipital lobes (improved at 6 mo)
IV ACV, IV GCV	...	Initial progression; stabilized over 2 w	OU	20/60	CF	Confusion, dysphasic episode, old internal capsule scars (MRI)
IV ACV, IV FOS, IVIT FOS	Famciclovir	Stabilized, then regressed, declined further treatment	OD	NLP	NLP	Subacute dementia, CT negative, seizures
IV ACV, IV FOS, IVIT GCV, IVIT FOS	...	Progressive decline over 2 mo	...	NLP	NLP	Left 6th cranial nerve palsy, sensory loss in right upper limb

vision OU (oculi unitas; 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 tuberculo-
 sis, 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/ μ L.

In December 1994, coincident with a culture-positive recur-
 rence 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.

Variable	No. (%) of patients (<i>n</i> = 11)
No. of eyes involved	20 (91)
Age: mean; median (y)	34; 36
Sex	
Male	7 (64)
Female	4 (36)
HIV risk factor	
Homosexuality	4
Heterosexuality	2
Intravenous drug abuse	3
Hemophilia	1
Unknown	1
No. of CD4 cells per μ L: range; median	5–85; 12
Prior VZV infection	8 (73)
Prior recurrent HSV infection	4 (36)
Concurrent CMV retinitis (<i>n</i> = 20)	3 (15)
Presenting symptom(s) in worse eye	
Blurring: central visual loss	9 (82)
Peripheral/paracentral visual field loss	2 (18)
Pain	3 (27)
Flashes and floaters	2 (18)
Retinal detachment in involved eyes (<i>n</i> = 20)	14 (70)
Onset (median, 2 w after presentation)	
At presentation	4
≤ 2 w	1
2–6 w	9

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 \cdot dl] 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.

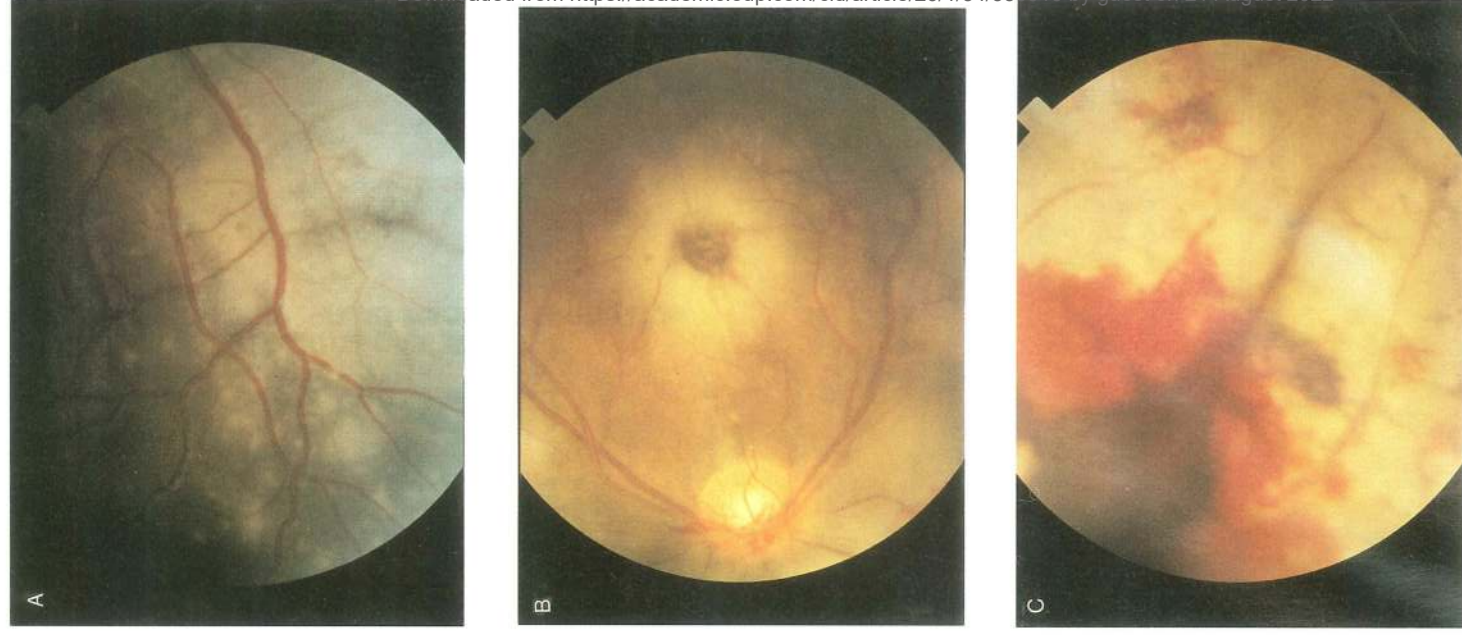


Figure 1. Rapidly progressive herpetic necrotizing retinitis (RPHNR) in patient 9. *A*, right eye: multifocal outer retinal opacification involving entire inferior retina, with early macular involvement (not shown). Visual acuity, 20/70. *B*, left eye: focus of classical RPHNR central macular involvement. 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.



Figure 2. Patient 1: neurosensory retina and retinal pigment epithelium of the posterior pole display profound postmictotic atrophy. The internal limiting membrane (arrows) of the retina rests within $40\ \mu$ of Bruch's membrane (arrowheads). No glial or neuroepithelial elements are left—only pigment-filled macrophages and extracellular melanin pigment (stain, hematoxylin-eosin; original magnification, $\times 430$).

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 feathery 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

opaque (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 ($15\ \text{mg}/[\text{kg} \cdot \text{d}]$) and foscarnet ($120\ \text{mg}/[\text{kg} \cdot \text{d}]$). Alternating three-times-a-week intraocular injections of ganciclovir ($2,000\ \mu\text{g}$) and foscarnet ($2,400\ \mu\text{g}$) 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, $1,000\ \mu\text{g}$; foscarnet, $1,200\ \mu\text{g}$).

The viral retinitis became quiescent OD, with a visual acuity of 20/150. She died 2 months after the development of RPHRN.

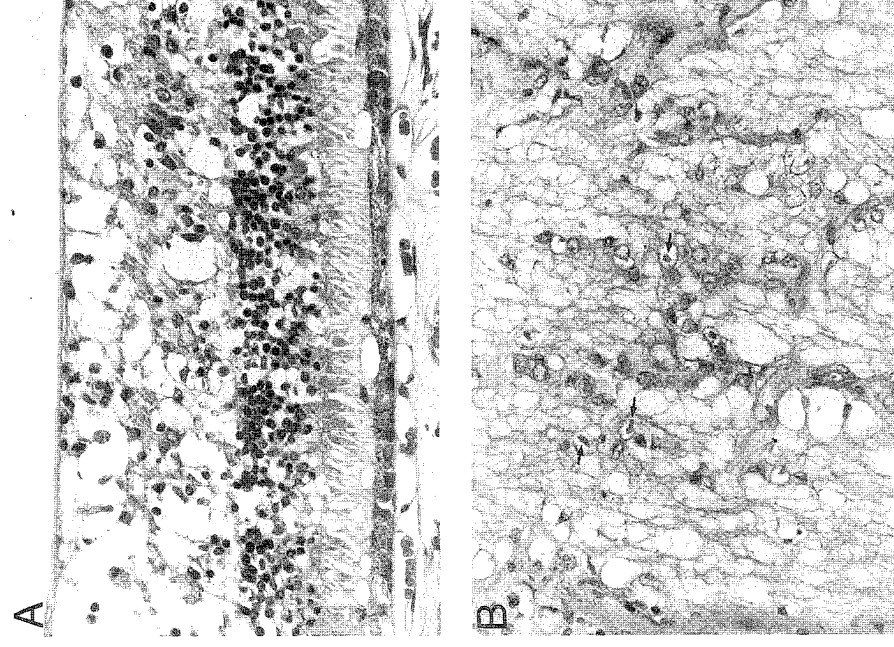


Figure 3. Patient 2: *A*, posterior pole of the left eye showing severe necrosis of the inner retina, with almost no signs of inflammation. The outer nuclear layer photoreceptors and retinal pigment epithelial cells are relatively undisturbed at this stage of the infection. *B*, the optic nerve, ~ 1 mm behind the lamina cribrosa, shows numerous glial cells with nuclear inclusion bodies (arrows). (Stain, hematoxylin-eosin; original magnification, $\times 430$.)

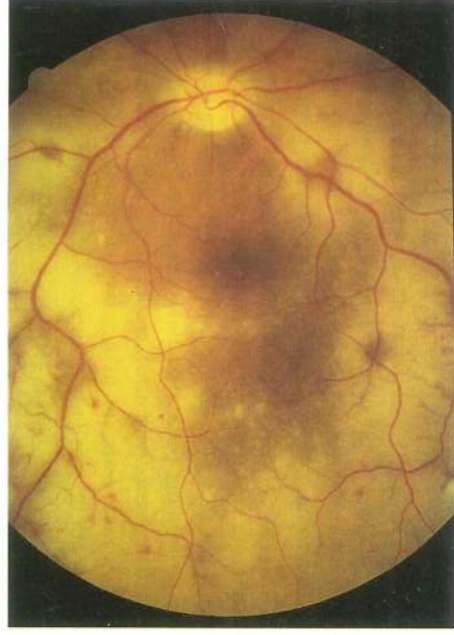


Figure 4. Case 1 (patient 3): severe RPHRN OD, with presumed optic nerve involvement (visual acuity: light perception). Within 3 weeks, the patient lost light perception in both eyes.

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 $50/\mu\text{L}$ 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 circumfer-

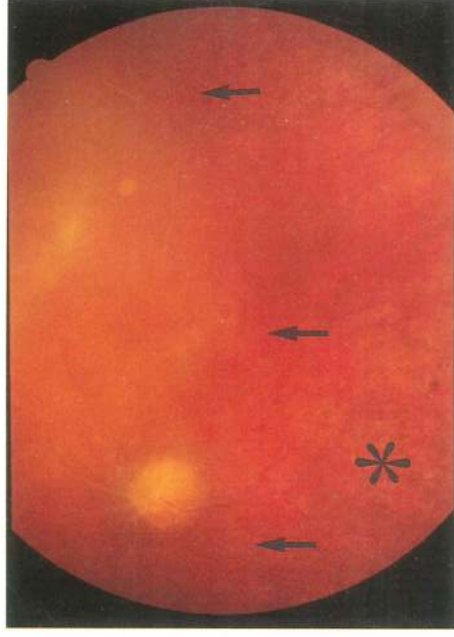


Figure 6. Case 3 (patient 6): atypical milky opacification of retina OS diffusely involved with RPHRN, believed to be caused by HSV (per clinical evidence). Visual acuity: 20/100. The inferior retinal periphery is scarred by old CMV retinitis (*asterisk*) and delimits the area of retinal necrosis (*arrows*).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

ential, 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 $\mu\text{g}/0.1\text{ mL}$) and foscarnet (2,400 $\mu\text{g}/0.1\text{ mL}$). 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 intraocular 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/mL with administration of saquinavir (Invirase; Roche, Nutley, NJ), started after stabilization of the RPHRN.

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 $10/\mu\text{L}$. Her



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.

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 T₂ 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, bilateral-ity, 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 sensory 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 perivascular 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]. Moorthy 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. Intra-neuronal [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 involvement 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], meningomyelodradiculitis caused by necrotizing CNS vasculitis [45, 50], and leptomeningitis 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 3, 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 intraocular 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 immunocompetent 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 investi-

gated. 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, foscarnet is the logical primary therapy. Foscarnet 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 foscarnet (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; Burroughs-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

- Holland GN, Tufail A, Jordan MC. Cytomegalovirus diseases. In: Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular infection and immunity*. St. Louis: Mosby, 1996:1088–129.
- Forster DJ, Dugel PU, Frangieh GT, Liggett PE, Rao NA. Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1990;110:341–8.
- Yoser SL, Forster DJ, Rao NA. Systemic viral infections and their retinal and chorooidal manifestations. *Surv Ophthalmol* 1993;37:313–52.
- Kulbertson WW, Dix RD. Varicella-zoster virus diseases: posterior segment of the eye. In: Pepose JR, Holland GN, Wilhelmus KR, eds. *Ocular infection and immunity*. St. Louis: Mosby, 1996:1131–54.
- Margolis TP, Atherton SS. Herpes simplex virus diseases: posterior segment of the eye. In: Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular infection and immunity*. St. Louis: Mosby, 1996:1155–67.
- Opremacak EM. Other viral infections of the retina. In: Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular infection and immunity*. St. Louis: Mosby, 1996:1169–82.
- Holland GN, Executive Committee of the American Uveitis Society. Standard diagnostic criteria for the acute retinal necrosis syndrome. *Am J Ophthalmol* 1994;117:663–6.
- Duker JS, Blumenkranz MS. Diagnosis and management of the acute retinal necrosis (ARN) syndrome. *Surv Ophthalmol* 1991;35:327–43.
- Maandell BA, Sternberg P. The acute retinal necrosis syndrome. In: Lewis H, Ryan SJ, eds. *Medical and surgical retina: advances, controversies, and management*. St. Louis: Mosby, 1994:400–14.
- Blumenkranz MS, Culbertson WW, Clarkson JG, Dix R. Treatment of the acute retinal necrosis syndrome with intravenous acyclovir. *Ophthalmology* 1986;93:296–300.
- Freeman WR, Thomas EL, Rao NA, et al. Demonstration of herpes group virus in acute retinal necrosis syndrome. *Am J Ophthalmol* 1986;102:701–9.
- Jabs DA, Schachar AP, Liss R, Knox DL, Michels RG. Presumed varicella zoster retinitis in immunocompromised patients. *Retina* 1987;7:9–13.
- Chess J, Marcus DM. Zoster-related bilateral acute retinal necrosis syndrome as presenting sign in AIDS. *Ann Ophthalmol* 1988;20:431–5, 438.
- Fabricius E-M, Lipp T, Kaboth W. Akute Retinaneurose und Herpes-Enzephalitis: Schlüsselrolle des Augenarztes bei der Diagnose opportunistischer Infektionen bei AIDS, erfolgreiche Therapie mit Acyclovir (Zovirax). *Klin Monatsbl Augenheilkd* 1990;196:160–5.
- Margolis TP, Lowder CY, Holland GN, et al. Varicella-zoster virus retinitis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1991;112:119–31.
- Pfaffl W, Fabricius E-M, Scheidegger K, Brommer M. Akute Retinaneurose (ARN) und HIV-Infektion. *Fortschr Ophthalmol* 1991;88:705–11.
- Culbertson WW, Atherton SS. Acute retinal necrosis and similar retinitis syndromes. *Int Ophthalmol Clin* 1993;33(winter):129–43.
- Heilinger WC, Bolling JP, Smith TF, Campbell RJ. Varicella-zoster virus retinitis in a patient with AIDS-related complex: case report and brief review of the acute retinal necrosis syndrome. *Clin Infect Dis* 1993;16:208–12.
- Sellitti TP, Huang AJW, Schifflin J, Davis JL. Association of herpes zoster ophthalmicus with acquired immunodeficiency syndrome and acute retinal necrosis. *Am J Ophthalmol* 1993;116:297–301.
- Friedman SM, Mames RN, Sleasman JW, Whitecup SM. Acute retinal necrosis after chickenpox in a patient with acquired immunodeficiency syndrome. *Arch Ophthalmol* 1993;111:1607–8.
- Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992;41(suppl RR-17):1–19.
- Connelly BL, Stanberry LR, Bernstein DJ. Detection of varicella-zoster virus DNA in nasopharyngeal secretions of immune household contacts of varicella. *J Infect Dis* 1993;168:1253–5.
- Friedman SM, Margo CE, Connelly BL. Varicella-zoster virus retinitis as the initial manifestation of the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1994;117:536–8.
- Pavan PR, Menosky MM. Progressive outer retinal necrosis treated with repeated, high dose, intravitreal, antiviral injections as well as systemic therapy. *The Vitreous Society Online Journal* [serial online] 1996–1997 [cited 1997 Jan 9];1:14 screens]. Available from URL: <http://www.vitreousociety.org/index.htm>
- Easty DL. Virus disease of the eye. Chicago: Year Book Publishers, 1985:153.
- Johnston WH, Holland GN, Engstrom RE Jr, Rimmer S. Recurrence of presumed varicella-zoster virus retinopathy in patients with acquired immunodeficiency syndrome. *Am J Ophthalmol* 1993;116:42–50.
- Engstrom RE Jr, Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome: a variant of necrotizing herpetic retinopathy in patients with AIDS. *Ophthalmology* 1994;101:1488–502.
- Kuppermann BD, Quiceno JJ, Wiley C, et al. Clinical and histopathologic study of varicella zoster virus retinitis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1994;118:589–600.
- Moorthy RS, Weinberg DV, Tetch SA, et al. Management of varicella zoster virus retinitis in AIDS. *Br J Ophthalmol* 1997;81:189–94.
- Garweg J, Böhnke M. Varicella-zoster virus is strongly associated with atypical necrotizing herpetic retinopathies. *Clin Infect Dis* 1997;24:603–8.
- Pavesio CE, Mitchell SM, Barton K, Schwartz SD, Towler HMA, Lightman S. Progressive outer retinal necrosis (PORN) in AIDS patients: a different appearance of varicella-zoster retinitis. *Eye* 1995;9:271–6.
- Greven CM, Ford J, Stanton C, et al. Progressive outer retinal necrosis secondary to varicella-zoster virus in acquired immune deficiency syndrome. *Retina* 1995;15:14–20.
- Galindez OA, Sabates NR, Whitacre MM, Sabates FN. Rapidly progressive outer retinal necrosis caused by varicella-zoster virus in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1996;22:149–51.
- Luyendijk L, van der Horn GJ, Visser OHE, et al. Detection of locally produced antibodies to herpes viruses in the aqueous of patients with acquired immune deficiency syndrome (AIDS) or acute retinal necrosis syndrome (ARN). *Curr Eye Res* 1990;9(suppl):7–11.
- Cunningham ET Jr, Short GA, Irvine AR, Duker JS, Margolis TP. Acquired immunodeficiency syndrome-associated herpes simplex virus retinitis: clinical description and use of a polymerase chain reaction-based assay as a diagnostic tool. *Arch Ophthalmol* 1996;114:834–40.
- Duker JS, Nielsen JC, Eagle RC Jr, Bosley TM, Granadter R, Benson WE. Rapidly progressive acute retinal necrosis secondary to herpes simplex virus, type 1. *Ophthalmology* 1990;97:1638–43.
- Cohen PR, Beltrani VP, Grossman ME. Disseminated herpes zoster in patients with human immunodeficiency virus infection. *Am J Med* 1988;84:1076–80.
- Reske-Nielsen E, Oster S, Pedersen B. Herpes zoster ophthalmicus and the mesencephalic nucleus: a neuropathological study. *Acta Pathol Microbiol Immunol Scand* 1986;94A:263–9.
- Rostaad SW, Olson K, McDougall J, Shaw C-M, Alvord EC Jr. Transsynaptic spread of varicella-zoster virus through the visual system: a mechanism of viral dissemination in the central nervous system. *Hum Pathol* 1989;20:174–9.
- Shayegani A, Odel JG, Kazim M, Hall LS, Bamford N, Schubert H. Varicella-zoster virus retrobulbar optic neuritis in a patient with human immunodeficiency virus. *Am J Ophthalmol* 1996;122:586–8.
- Streitlen JW. Regional immunology of the eye. In: Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular infection and immunity*. St. Louis: Mosby, 1996:19–32.
- Rousseau F, Perronne C, Raguin G, et al. Necrotizing retinitis and cerebral vasculitis due to varicella-zoster virus in patients infected with the human immunodeficiency virus [letter]. *Clin Infect Dis* 1993;17:943–4.

43. van den Horn GJ, Meenken C, Troost D. Association of progressive outer retinal necrosis and varicella zoster encephalitis in a patient with AIDS. *Br J Ophthalmol* **1996**;80:982-5.
44. Petit CK, Cho E-S, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol* **1986**;45:635-46.
45. Gray F, Bélec L, Lesses MC, et al. Varicella-zoster virus infection of the central nervous system in the acquired immune deficiency syndrome. *Brain* **1994**;117:987-99.
46. Gray F, Mohr M, Rozenberg F, et al. Varicella-zoster virus encephalitis in acquired immunodeficiency syndrome: report of four cases. *Neuropathol Appl Neurobiol* **1992**;18:502-14.
47. Moulignier A, Pialoux G, Dega H, Dupont B, Huere M, Baudrimont M. Brain stem encephalitis due to varicella-zoster virus in a patient with AIDS. *Clin Infect Dis* **1995**;20:1378-80.
48. Gilden DH, Beinlich BR, Rubinstein EM, et al. Varicella-zoster virus myelitis: an expanding spectrum. *Neurology* **1994**;44:1818-23.
49. Lionnet F, Pulik M, Genet P, et al. Myelitis due to varicella-zoster virus in two patients with AIDS: successful treatment with acyclovir. *Clin Infect Dis* **1996**;22:138-40.
50. Chrétien F, Gray F, Lesses MC, et al. Acute varicella-zoster virus ventriculitis and meningo-myelo-radiculitis in acquired immunodeficiency syndrome. *Acta Neuropathol* **1993**;86:659-65.
51. Gulick R. Varicella-zoster virus infection in HIV disease. *Opportun Com-plic HIV* **1994**;3:58-69.
52. Pinnolis MK, Foxworthy D, Kemp B. Treatment of progressive outer retinal necrosis with sorivudine. *Am J Ophthalmol* **1995**;119:516-7.
53. Morley MG, Duker JS, Zaeks C. Successful treatment of rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome. *Am J Ophthalmol* **1994**;117:264-5.
54. The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the cytomegalovirus retreatment trial. *Arch Ophthalmol* **1996**;114:23-33.
55. Palay DA, Sternberg P Jr, Davis J, et al. Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. *Am J Ophthalmol* **1991**;112:250-5.
56. Crapotta JA, Freeman WR, Feldman RM, et al. Visual outcome in acute retinal necrosis. *Retina* **1993**;13:208-13.
57. Walton RC, Byrnes GA, Chan C-C, Nussenblatt RB. Fluorescein angiography in the progressive outer retinal necrosis syndrome. *Retina* **1996**;16:393-8.
58. Jacobson MA, Berger TG, Fikrig S, et al. Acyclovir-resistant varicella-zoster virus infection after chronic oral acyclovir therapy in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* **1990**;112:187-91.
59. Safran S, Berger TG, Gilson I, et al. Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* **1991**;115:19-21.
60. Talarico CL, Phelps WC, Biron KK. Analysis of the thymidine kinase genes from acyclovir-resistant mutants of varicella-zoster virus isolated from patients with AIDS. *J Virol* **1993**;67:1024-33.
61. Wunderl W, Miner R, Wintsch J, von Gunten S, Hirsch HH, Hirschel B. Outer retinal necrosis due to a strain of varicella-zoster virus resistant to acyclovir, ganciclovir, and sorivudine. *Clin Infect Dis* **1996**;22:864-5.
62. Balfour HH Jr, Benson C, Braun J, et al. Management of acyclovir-resistant herpes simplex and varicella-zoster virus infections. *J Acquir Immune Defic Syndr* **1994**;7:254-60.
63. Safran S, Assaykeen T, Follansbee S, Mills J. Foscarnet therapy for acyclovir-resistant mucocutaneous herpes simplex virus infection in 26 AIDS patients: preliminary data. *J Infect Dis* **1990**;161:1078-84.
64. Hardy WD. Foscarnet treatment of acyclovir-resistant herpes simplex virus infection in patients with acquired immunodeficiency syndrome: preliminary results of a controlled, randomized, regimen-comparative trial. *Am J Med* **1992**;92(suppl 2A):30S-5S.
65. Spaide RF, Martin DF, Teich SA, Katz A, Toth I. Successful treatment of progressive outer retinal necrosis syndrome. *Retina* **1996**;16:479-87.