Retinal and Choroidal Manifestations of Viral Diseases

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Abstract

Several viral infections may involve the retina and choroid. These viruses include herpesviruses, rubella, rubeola, influenza, Epstein-Barr virus, human immunodeficiency virus (HIV), and West Nile virus. The predominant causes of viral retinitis and choroiditis are viruses of the Herpesviridae family. Classic findings of infection include vitritis, periarteritis, necrotizing retinitis, and optic neuropathy.

Keywords

Choroiditis • Cytomegalovirus • Herpes simplex • Herpesviridae infections • Influenza • Retinitis • Varicella zoster • West Nile virus

Introduction

Several viral infections may involve the retina and choroid. These viruses include herpes viruses, rubella, rubeola, influenza, Epstein-Barr virus, human immunodeficiency virus (HIV), and West Nile virus. The predominant causes of viral retinitis and choroiditis are viruses of the Herpesviridae family. Classic findings of infection include vitritis, periarteritis, necrotizing retinitis, and optic neuropathy. The central questions regarding the diagnosis and management of viral infections of the retina include identification of the best method of rapid and specific treatment, the optimal surgical approach for repair of secondary retinal detachment, and the primary etiology of ocular infection and reactivation especially in the case of latent virus within the central nervous system.

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Acute Retinal Necrosis

In Japan, in 1971, Urayama et al. reported six cases of a novel form of uveitis and named the disease Kirisawa's uveitis. Later, Willerson reported a necrotizing vaso-occlusive retinitis and named this syndrome acute retinal necrosis (ARN) [1]. In 1982, Culbertson identified the

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causative organism of ARN as herpesvirus, first by demonstrating the presence of intraocular herpesvirus particles by electron microscopy and later by culturing varicella-zoster virus (VZV) from an affected eye [2].

ARN is an ocular emergency as it rapidly leads to blindness if not promptly recognized and treated. It is characterized by peripheral necrotizing retinitis, retinal arteritis, and intraocular inflammation. ARN syndrome is caused by a primary infection with [3] or reactivation of a latent herpes simplex virus (HSV-1 or HSV-2) or varicella-zoster virus (VZV). While advances have been made in the diagnosis of ARN syndrome, specifically with the detection of viral DNA in intraocular fluids using polymerase chain reaction (PCR), recognition of the disease remains based on clinical appearance.

In 1994, the American Uveitis Society published a set of diagnostic criteria for ARN (Fig. 8.1): (1) one or more foci of retinal necrosis with discrete borders in the peripheral retina, (2) rapid progression in the absence of antiviral therapy, (3) circumferential spread, (4) occlusive vasculopathy with arteriolar involvement, (5) prominent vitritis and anterior chamber inflammation, and (6) optic neuropathy or atrophy, scleritis, and pain (supportive but not required). It should be noted that this definition does not depend on the extent of necrosis, viral etiology, or immune status of the host. When these criteria are not met in the setting of necrotizing retinitis that additionally does not resemble cytomegalovirus (CMV) retinitis or progressive outer retinal necrosis (PORN), the term "necrotizing herpetic retinopathy" is suggested. Necrotizing herpetic retinopathy can occur early after the initial infection. However, in this circumstance, the retinal lesion is usually localized and slowly progressive, whereas in ARN the lesions are rapidly progressive [4].

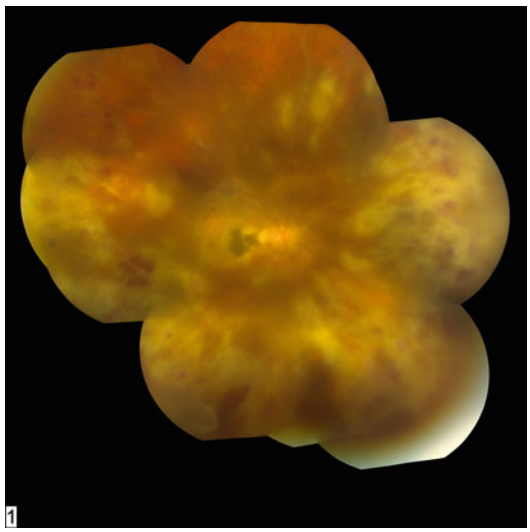

Fig. 8.1 Acute retinal necrosis. Photograph demonstrates retinal necrosis, vitritis, and perivascular infiltrates

Causative Virus

The causative agents in ARN are the alpha herpes viruses HSV-1, HSV-2, VZV, and rarely CMV [5]. These viruses have been isolated from the choroid [6], retina [6], lens, and vitreous body [6–8]. Antigen for HSV-1 had been detected in the inflammatory infiltrate and also in the retina and vitreous body [9, 10]. Antigen for HSV-2 has been detected in the vitreous [11] and also in the spinal fluid and serum [12, 13]. DNA for HSV-1 and HSV-2 has been amplified by PCR in several ocular biopsies [14–18]. Interestingly, a study measuring the serum anti-HSV antibody titers by enzyme-linked immunosorbent assay (ELISA) revealed a positive anti-HSV-2 antibody and negative anti-HSV-1 antibody in the sera of a group of Japanese patients with HSV-2 DNA–positive ARN syndrome [12]. This finding that patients who are positive for HSV-2 ARN only possess anti-HSV-2 antibodies suggests that the absence of preexisting HSV-1 infection may play an important role in the development of HSV-2 ARN syndrome.

Epidemiology

ARN is a rare condition. A study from the United Kingdom demonstrated an incidence of 1 in every 1.6–2 million people per year [19]. Additionally, a 2002 study revealed that only 41 (1.3%) of 3,060 Japanese uveitis patients had ARN [20].

There is controversy regarding the discrepancy of sex with the development of ARN. One study reports no sex difference for all types of ARN and the prevalence of ARN is nearly equal between the sexes [16]. HSV-2-associated ARN tends to occur at a younger age than HSV-1- and VZV-associated ARN. In one report, the mean age of onset was 20 years (6 cases) for HSV-2–ARN, 47 years (7 cases) for HSV-1–ARN, and 57 years (13 cases) for VZV–ARN syndrome [16].

Virological Diagnosis

Virological analysis of the aqueous humor or vitreous is required for diagnostic confirmation and for identification of the specific herpes virus. The highest sensitivity and specificity are obtained through the detection of viral DNA by PCR. Real-time quantitative PCR has allowed monitoring of viral titer and treatment response throughout the clinical course of ARN. There have been reports of patients with ARN in whom real-time PCR documented a decrease in the HSV DNA copy number in aqueous humor following the initiation of treatment [21, 22].

Since most adults have a history of infection by herpes virus, the presence of viral antibodies in the peripheral blood is not a specific finding. Additionally, the serum antibody level does not necessarily correlate with clinical activity of the virus, specifically with ARN [23]. However, comparison between the antibody load in serum and intraocular fluids may be measured and compared to monitor intraocular viral infection. The ratio of specific antibody (aqueous or vitreous)/total IgG (aqueous or vitreous) to specific antibody (serum)/total IgG (serum) makes up the Goldmann-Witmer coefficient. If the coefficient is 1 or greater, theoretically, there is intraocular production of antibody, indicating an intraocular propagation of the virus. In practice, a coefficient of 4 or above is interpreted as intraocular infection, whereas a coefficient between 1 and 4 is suspected infection and any coefficient below 1 is regarded as negative. In general, these strategies are mired by complexities in the course of antibody production, which is weak in early infection and therefore calculations must be normalized against IgG production. PCR should be chosen as the initial test for suspected cases, and antibody titers should be reserved for cases with a time lapse from onset. It is important to note, though, that treatment should never await diagnostic confirmation when there is strong suspicion based on clinical examination.

Clinical Course

ARN is predominantly unilateral, but the contralateral eye occasionally becomes involved, usually within 1–6 weeks following onset in 9–36% of patients. A national population-based study from the United Kingdom revealed that 9.7% of subjects had progression to the contralateral eye [19]. While Palay et al. reported that prolonged acyclovir treatment decreases the involvement of the contralateral eye, another study reported that 9 of 80 patients (11.3%) had contralateral involvement despite adequate antiviral therapy [24, 25].

The cardinal symptoms of ARN include acute onset of ocular pain, external vasodilatation, unilateral loss of vision, photophobia, and floaters. The classic triad of symptoms includes vitritis, multifocal yellow-white peripheral retinitis, and retinal arteriolitis. In some cases, early manifestations of choroiditis can be observed as opacification of the choroid/retinal pigment epithelium (RPE) with hypoperfusion then late staining of the choroid followed by the classic findings [26]. Heavy anterior chamber and vitreous inflammation is frequently observed during the acute phase. Vitreous inflammation soon resolves following treatment initiation, but opacity can recur 3–4 weeks after onset due to fibrous organization of the vitreous. This can lead to incomplete posterior vitreous detachments, proliferative vitreoretinopathy, and persistent vitreous traction of vitritis, periarteritis, necrotizing retinitis, and optic neuropathy.

Multifocal, small, white-yellow granular lesions develop in the peripheral retina, considered to be a result of active viral proliferation and excessive recruitment of immune response in outer retinal layers. These lesions are usually discontinuous

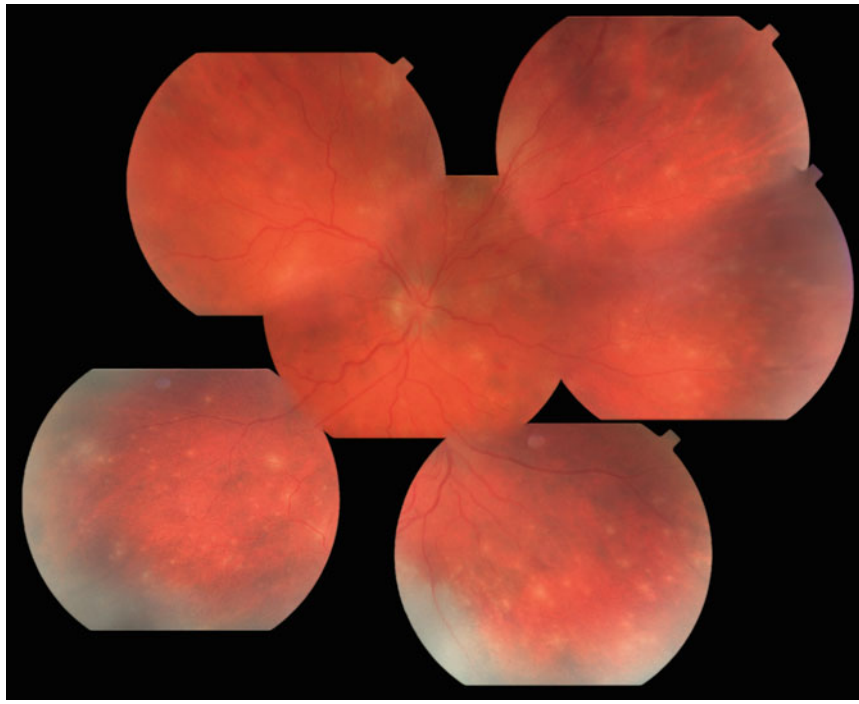

Fig. 8.2 Multifocal posterior necrotizing retinitis. Montage demonstrates punctate multifocal lesions that will coalesce to confluent areas of retinitis. This variant of ARN is often associated with varicella zoster

with scalloped edges. As the disease progresses, these lesions enlarge and coalesce to become confluent, dense, creamy opaque lesions which eventually spread toward the posterior pole. Periarteritis and occlusive retinal vasculitis are also commonly observed, sometimes associated with the development of ghost vessels and club-shaped hemorrhages along the vasculature [27]. As the disease advances, full-thickness retinal necrosis develops. Circulatory impairment in the retinal tissue surrounding the early granular lesions likely occurs early in the clinical course. Even with the initiation of treatment, these lesions may expand, leading to a several-day lag time between treatment initiation and disease regression. As the vitreous contracts from chronic inflammation, even weak traction on the retina can create breaks where necrosis has occurred. In the final stages and even after regression, retinal detachment occurs at rate of 50–75% secondary to breaks in these areas of retinal necrosis. Margolis et al. reported herpetic retinitis presenting as a rapidly progressive multifocal posterior necrotizing retinitis caused mostly by varicella-zoster virus. Patients with this clinical presentation had a 100% incidence of rhegmatogenous retinal detachment (Fig. 8.2) [28].

Treatment

Treatment of ARN has three general principles: rapid administration of antiviral therapy, protection of the uninvolved eye, and surveillance/repair of retinal detachment. The most important action is immediate initiation of intravenous (IV) acyclovir (10 mg/kg body weight every 8 h), usually with the assistance of infectious disease consultation. This medication may lead to reversible elevations in serum creatinine and liver function tests, and dosage should be reduced in the presence of renal insufficiency. Additional therapy with intravitreal injection of ganciclovir (0.2–2.0 mg/0.1 mL) or foscarnet (1.2–2.4 mg/0.1 mL) is recommended at presentation. This should immediately follow vitreous aspirate for PCR studies but should not await laboratory confirmation. These drugs have a short

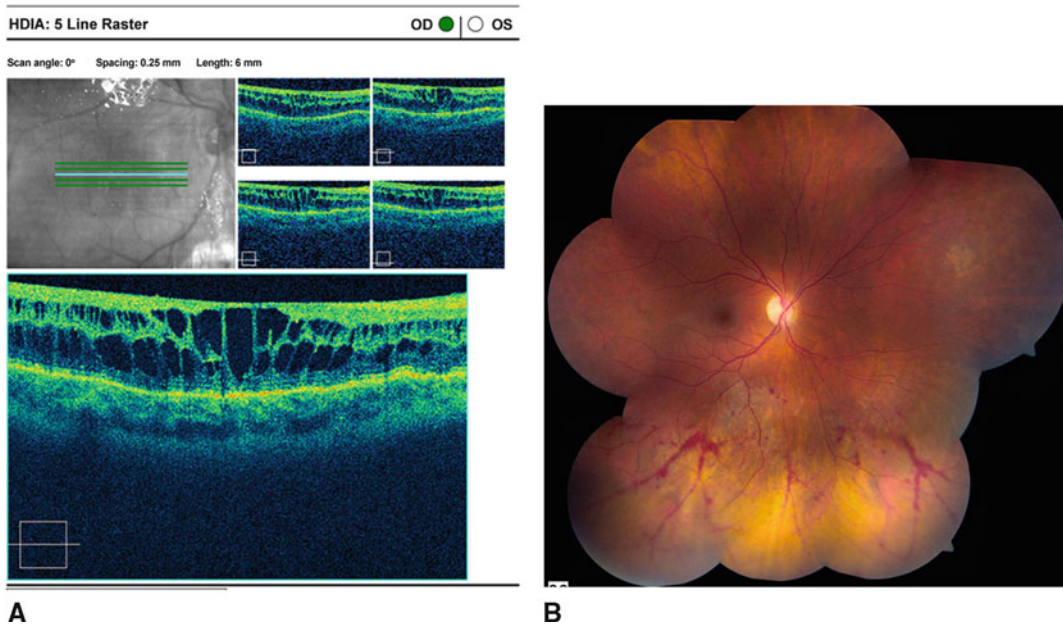

Fig. 8.3 Optical coherence tomography (**a**) shows massive cystoid macular edema in a patient with acute retinal necrosis (**b**). At presentation, the patient had received 2 weeks of intravenous acyclovir for herpes simplex encephalitis

half-life and intravitreal injection may need to be repeated twice weekly until adequate control has been obtained. With the advent of intravitreal injections, initial combination therapy with the oral prodrug, valacyclovir (1–2 g orally three times daily), has been used as first-line therapy or in patients who fail to respond to IV acyclovir. There is currently no randomized trial that compares IV to oral therapy, and presently, the cost of the oral prodrug is 10–100 times the cost of generic acyclovir. Hence, 2 weeks of outpatient IV therapy followed by oral acyclovir may be more cost effective. Following 24–48 h of systemic antiviral therapy, systemic corticosteroid, predominantly prednisone (1 mg/kg/day), is initiated to treat the associated inflammation.

The second area of controversy is the optimal timing for conversion to oral therapy when IV therapy is used and the general time period for maintenance therapy. Usually following a 10–14-day course of IV acyclovir with or without weekly intravitreal antiviral injections, treatment may be changed to oral therapy if adequate regression of retinitis is observed. Oral acyclovir is rarely used secondary to its poor bioavailability. Instead, valacyclovir (1 g three times daily for VZV; 500 mg daily for HSV) or famciclovir (500 mg three times daily for VZV; 250 mg three times daily for HSV) is initiated for at least 3 months following infection. If central nervous system manifestations are noted that are consistent with viral meningitis or encephalitis, management requires a longer course of IV therapy and perhaps even long-term viral suppression with oral antiviral therapy.

Even following "resolution" of ARN, there is nearly a 75% risk of retinal detachment. Prophylactic barrier laser photocoagulation should be applied to areas of healthy retina posterior to necrosis as soon as vitreous inflammation clearance permits an adequate view. Additionally, early pars plana vitrectomy along with endolaser treatment has been postulated to have better response secondary to removal of contributing vitreous traction. Generally, in the presence of multiple retinal breaks with or without detachments, reattachment by vitrectomy with either C3F8 or silicone oil injection is usually necessary. Although the rate of reattachment approaches 98%, by either gas or silicone, a visually limiting complication of ARN is cystoid macular edema (CME) (Fig. 8.3a, b), which can be difficult to treat secondary to the threat of viral reactivation with intensive steroid

treatment. In severe circumstances, one may consider the placement of a sustained-release ganciclovir implant (Vitrasert®, Bausch & Lomb, Madison, NJ, USA) with continued oral antiviral treatment if intravitreal triamcinolone acetonide is necessary to resolve the CME or if a retinal detachment repair is necessary. The Vitrasert® implant can be used in conjunction with either silicone oil or C3F8.

The prognosis for ARN is generally poor. The majority of patients have less than 20/200 vision in the affected eye. However, the prognosis may significantly improve with early recognition, aggressive antiviral therapy, and laser photocoagulation. In severe cases, especially with retinal detachment, hypotony is an infrequent but serious complication.

Cytomegalovirus

Cytomegalovirus (CMV) is a herpes virus containing double-stranded DNA. Systemic infection is common and causes an antibody-negative mononucleosis syndrome. CMV retinitis is the most common ophthalmic manifestation of CMV, occurring as a congenital infection in infants or as an opportunistic infection in the immunocompromised host. Adults commonly affected include those individuals with acquired immunodeficiency syndrome (AIDS), oncology patients, and patients on immunosuppressive/immunomodulatory therapy post-organ transplantation or for autoimmune disorders. Specifically, AIDS patients with a CD4+ count lower than 50 cells/μ(mu)L are considered at highest risk and make up the most commonly affected population of patients. Ocular CMV infection is an especially rare cause of ARN in immunocompetent adults. The advent of highly active antiretroviral therapy (HAART), though, has significantly reduced incidence of CMV retinitis and its complications in AIDS patients.

Diagnosis

The diagnosis of CMV retinitis is primarily based on clinical findings in the immunocompromised host, with observation of characteristic hemorrhagic, full-thickness retinitis (Fig. 8.4a, b, c).

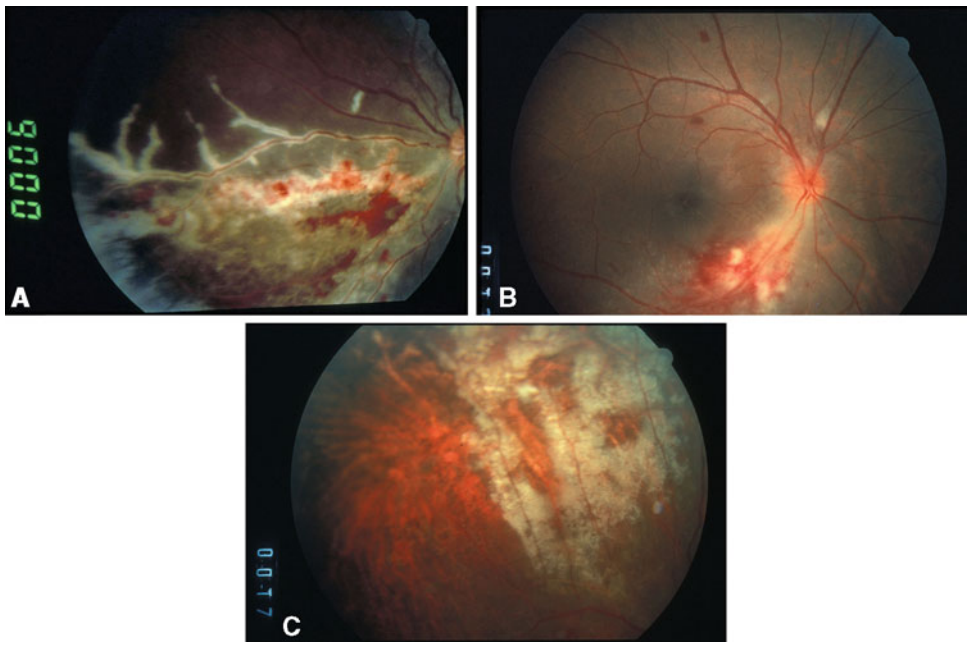

Fig. 8.4 Cytomegalovirus can present as a pattern of (**a**) frosted branch angiitis, (**b**) hemorrhagic retinitis, or (**c**) granular infiltrate

Early CMV may appear as a small white retinal infiltrate mistaken for a cotton-wool spot of HIV-related microvasculopathy. However, this focal edema quickly expands without treatment. The healthy retina becomes sharply demarcated from spreading infected retinal cells. Histopathology of infected retina reveals pathognomonic large eosinophilic intranuclear inclusions and small basophilic cytoplasmic inclusions and few surrounding inflammatory cells. Active retinitis has a faint granular border of intraretinal infiltrates that represent foci of viral activity in the normal retina. Infected cells lyse, leaving an area of full-thickness necrosis with underlying choroiditis. Released virus particles and cell-to-cell transmission allow infection of adjacent retinal cells. A diminished inflammatory response is observed secondary to the immunocompromised state of the host.

The identification of these clinical features relies on fundus photography, fluorescein angiography, optical coherence tomography, and electrophysiological testing. Fundus autofluorescence imaging can be helpful in highlighting areas of active CMV retinitis. A hyperautofluorescent signal has been correlated with flagrant advancing CMV retinitis, and a hyperautofluorescent border is helpful in the detection and localization of subtle CMV reactivation. In one of nine patients in a recent study, diffuse, punctate hyperautofluorescence after intravitreal ganciclovir and foscarnet was associated with medication-related toxicity [29].

Congenital CMV retinitis has a similar clinical appearance on ophthalmoscopic exam. However, it is additionally associated with systemic findings of jaundice, hepatosplenomegaly, ventriculomegaly with periventricular calcifications, petechial rash, seizures, microcephaly, fever, thrombocytopenia, anemia, and pneumonitis.

Staging and Progression

CMV retinitis staging is tied closely with the nature of CMV retinitis progression. The broadest staging classification focuses on the differentiation of active infectious retinitis from necrosis. There are three distinct variants of CMV retinitis: (1) classic or fulminant retinitis with large areas of retinal hemorrhage along a whitened, edematous, or necrotic retina, usually in the posterior pole in the distribution of the nerve fiber layer along the vascular arcades; (2) granular or indolent retinitis without retinal edema, hemorrhage, or vascular sheathing, progressing along active borders in the retinal periphery; and (3) perivascular CMV or frosted branch angiitis with retinal perivasculitis. Active CMV retinitis progresses in two modes. First, new discontinuous hemorrhagic skip lesions can appear, presumably through hematogenous spread. Second, and more commonly, lesions may expand and coalesce with nearby lesions via cell lysis and cell-to-cell transmission.

CMV retinitis may also be described by the zone of involvement. Zone 1 lies within 1,500 μ(mu)m of the optic nerve or 3,000 μm of the fovea, zone 2 extends from the edge of zone 1 to the vortex veins ampullae, and zone 3 extends from the edge of zone 2 to the ora serrata. Zones 2 and 3 are the most common sites of initial retinal involvement.

CMV retinitis lesions expand relatively slowly at 250–350 μm/week, and therefore, the center of the lesions will have time to progress from hemorrhagic to fully necrotic while the border remains active. This is an important contrast to ARN lesions which expand more rapidly usually without an identifiable atrophic center. When the central area progresses to necrotic tissue, the lesion evolves from an edematous hemorrhagic appearance to a glial scar with underlying retinal pigmented epithelium apparent. Therefore, special attention should be given to the edges of the lesions, inspecting for advancing retinitis, rather than central areas of atrophic and inactive infection, when monitoring for progression of infection.

Although this disease is destructive, prompt recognition and treatment of this slowly progressive infection can allow for visual preservation. The progression of CMV retinitis may be monitored by repeated clinical examinations or by serial fundus photography [30, 31]. Peripheral and/or central vision loss occurs predominantly

secondary to the development of an absolute scotoma due to retinal necrosis. It is common for patients to be asymptomatic until there is macular involvement with central vision loss. This may be secondary to necrosis involving the macula or to macular edema associated with nearby lesions. Additionally, if the optic nerve is involved, visual loss can be severe even with a minimal degree of retinitis.

Retinal detachment occurs in 5–29% of eyes in various case series, predominantly secondary to vitreous traction [32]. In those patients with retinal detachment in one eye, 50% will develop a detachment in the contralateral eye if involved in the disease course. The probability of retinal detachment increases, in a nonlinear manner, with the extent of retinal involvement. There is a fivefold increase in detachment incidence when the retinitis involves 25% of the retina compared to 10% involvement [33]. The risk of detachment is substantially less among patients receiving HAART, with an associated 60% reduction in retinal detachment rate ($P < .001$) [34]. The greatest benefit was observed among patients who developed an immunologic response with the initiation of this therapy. This is attributed to better control of infection, resulting in smaller, inactive lesions and therefore better healed and more adherent scars [35, 36]. In one study, a significant difference in the rate of retinal detachment was additionally found between eyes treated with systemic therapy only and those treated with implants, whether used as primary therapy or subsequent to using systemic anti-CMV therapy [37].

Laboratory Findings

The most important risk factor for CMV retinitis is immune dysfunction. The CD4+ count is used as a marker of immune dysfunction in patients infected with HIV, and patients are deemed at highest risk when CD4 count falls below 50 cells/uL. Because these patients may be asymptomatic with regard to CMV retinitis, scheduled ophthalmic screening, with frequency of dilated fundus exams (Table 8.1) based on CD4 count, should be performed.

Table 8.1 Scheduled ophthalmic screening for ocular CMV based on CD4 count

CD4+ >100 cells/uL	Little risk; screen yearly
CD4+ 50 to 100 cells/uL	At risk; screening examination every 6 months
CD4+ <50 cells/uL	High risk; 35% incidence of CMV retinitis; median time to diagnosis of CMV retinitis is 13 months; screen every 3 months

The presence of atypical features can sometimes make clinical diagnosis more difficult. As noted above, initial signs of CMV retinitis may resemble cotton-wool spots commonly observed in HIV retinopathy. Additionally, it may be clinically difficult to distinguish CMV retinitis from intraocular lymphoma, complicating diagnosis in some patients [38]. Patients with an atypical presentation or those individuals nonresponsive to antiviral therapy may undergo aqueous or vitreous biopsy with subsequent PCR analysis to confirm the diagnosis and differentiate infection from other herpetic etiologies as well as toxoplasmosis. This diagnostic evaluation, though, is rarely practiced. Systemic specimens can be obtained from blood buffy coat, semen, or urine. Detection of CMV in the blood by DNA PCR is most predictive of developing CMV disease [39]. Patients with AIDS who test positive will have over a 60% chance of developing CMV end-organ disease. An important consideration is that responders to ganciclovir prophylaxis convert to PCR negative with treatment. Compared to non-responders, survival is increased 2.4 times at 12 months. In congenital CMV infection, identification of viral inclusion bodies, a positive CMV culture, and supportive PCR analysis of urine, saliva, and subretinal fluid may be helpful in the diagnosis.

Treatment

Pharmacologic

There are two main objectives in the treatment of CMV retinitis. First, vigorous anti-CMV medication must be initiated to stop viral propagation.

Second, the host's immunologic status must be corrected. This almost always entails the initiation or adjustment of HAART therapy because the majority of the CMV patients are AIDS patients. The initiation of HAART and anti-CMV therapy simultaneously will prevent immune reactivation uveitis while HAART-induced immunologic recovery is taking place. If the patient is suffering from other systemic infectious diseases, such as tuberculosis, HAART initiation or alteration is often delayed until treatment for the infection is started. This serves to reduce the risk of systemic inflammatory reactions against the other pathogen.

In general, current therapies use a high induction dose of the anti-CMV medication to halt active disease followed by the introduction of HAART. Following response to therapy, the patient's anti-CMV therapy may be lowered to an effective maintenance dose. This maintenance dose may be continued indefinitely if the patient remains persistently immunocompromised. However, if the patient exhibits a stable immune recovery, discontinuation of maintenance anti-CMV medication is possible.

CMV retinitis itself, independent of CD4 count, viral load, and presence of HAART therapy, is associated with a higher mortality in AIDS patients. There is a clear mortality benefit with the initiation of anti-CMV therapy [40]. There are five medications that are approved for CMV infection: ganciclovir (intravenous, intravitreal, intraocular implant), foscarnet (intravenous, intravitreal), cidofovir (intravenous, intravitreal), fomivirsen (intravitreal), and valganciclovir (oral). Routes of delivery and adverse effect profiles vary. Ganciclovir is a prodrug which is triphosphorylated intracellularly to allow inhibition of viral DNA polymerase. Ganciclovir is virostatic so eradication of the infection relies on a functional immune system. Several studies have shown that a 14-day course of intravenous ganciclovir (5 mg/kg twice daily) can halt CMV retinitis with 90% of the patients reverting to a less active lesion [41]. Neutropenia is an important adverse side effect of treatment with ganciclovir. Until the development of granulocyte colony-stimulating factor as an adjuvant therapy, it was a dose-limiting toxicity. Neutropenia typically occurs during the second week of therapy, and dosing should be adjusted to maintain neutrophil counts of at least 500 cells/uL.

Valganciclovir is the L-valyl ester prodrug of ganciclovir. After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases. Valganciclovir is the most common choice for initial therapy secondary to its convenience, lower cost, and absence of complications associated with intravenous administration. Current standard of care consists of an induction phase with valganciclovir (900 mg PO bid for 2–3 week) or ganciclovir (5 mg/kg IV bid for 2–3 week) followed by maintenance with valganciclovir (900 mg PO qd) until the CD4+ count is above 100 cells/uL.

Foscarnet also inhibits viral DNA polymerase, but in a different manner than ganciclovir. It is effective against herpesviruses, and it also inhibits reverse transcriptase and therefore is inhibitory on the replication of HIV. It is administered intravenously (2×90mg/kg daily or 3×60mg/kg daily). Although it is not as toxic to bone marrow as ganciclovir, it is nephrotoxic and leads to abnormalities in serum calcium, phosphate, and magnesium levels. It cannot be used with other nephrotoxic drugs, such as amphotericin B. The systemic and ocular complications of AIDS trial (SOCA) have demonstrated that foscarnet and ganciclovir are equally effective in preventing CMV retinitis [42].

Cidofovir is effective in the treatment of CMV retinitis, but it has an increased adverse effect profile and is not orally bioavailable. Cidofovir is additionally associated with immune reactivation uveitis.

Intravitreal ganciclovir, foscarnet, and cidofovir are additionally available. However, while these modes of treatment are extremely effective for local retinitis, they do not cover extraocular systemic CMV, which may additionally be debilitating. In one of nine patients in a recent study, diffuse, punctate hyperautofluorescence after intravitreal ganciclovir and foscarnet was associated with medication-related toxicity [29].

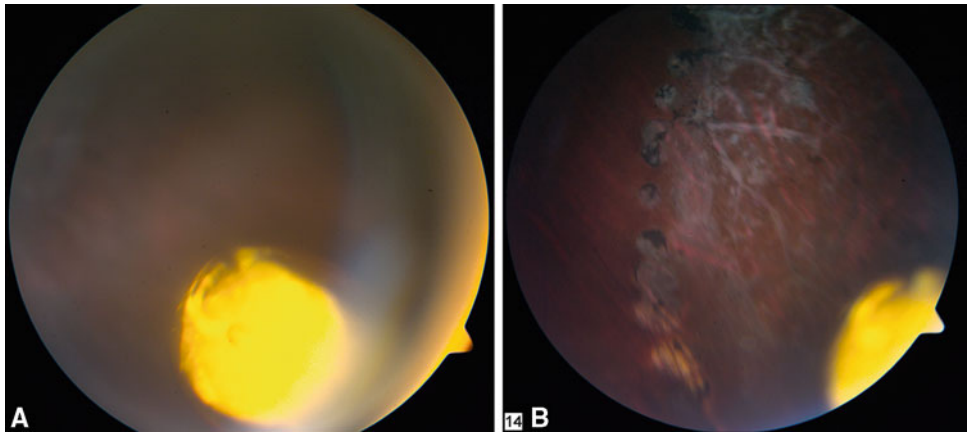

Fig. 8.5 Pars plana ganciclovir implant, Vitrasert (**a**) provides sustained delivery of intravitreal ganciclovir. (**b**) Laser was placed intraoperatively posterior to the broad temporal area of retinitis

Surgical

Intravitreal ganciclovir implant is used in patients who have reactivation of retinitis despite systemic treatment, or in those that cannot tolerate other treatments. The intravitreal ganciclovir implant (Vitrasert®) is an effective surgical modality for CMV treatment (Fig. 8.5a, b). It provides a 1 μg/h sustained release of ganciclovir over the course of 8 months [43, 44]. The implant is extremely important in patients who cannot tolerate systemic therapy, but does not address prophylaxis of the companion eye or systemic CMV viral load. Individuals with CMV retinitis commonly require surgical intervention for repair of a retinal detachment, and in this setting, concomitant vitrectomy and scleral buckle can be combined with ganciclovir implant. Retinal detachment occurs in 5–29% of eyes in various case series (Fig. 8.6) [32]. The total reattachment rate is 76%; macular attachment occurs in 90%. Mean postoperative visual acuity is 6/18. The risk of detachment is substantially less among patients receiving HAART. This is attributed to better control of infection, resulting in smaller, inactive lesions and therefore better healing.

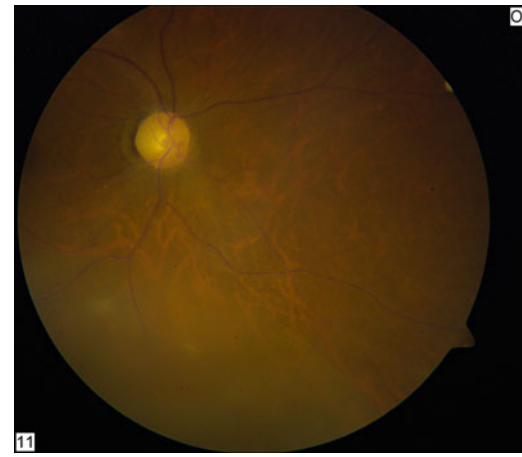

Fig. 8.6 Inferior, macula on, retinal detachment in a patient with CMV retinitis

CMV Retinitis and Therapy in the HAART Era

Highly active antiretroviral therapy (HAART) refers to the strategic combination of different classes of antiretroviral drugs which effectively suppress HIV replication. Treatment is marked by nearly complete clearing of HIV from the blood (decreasing viral load) and subsequent repletion of circulating CD4+ T lymphocytes. Immune recovery may require several months of therapy, during which time patients remain at risk for opportunistic infections. There are now approximately 30 FDA-approved antiretroviral drugs and fixed-drug combinations, summarized by the International AIDS Society-USA [45–47]. Before HAART became standard of care in HIV patients, CMV patients were required to take long-term maintenance doses of anti-CMV treatment and still unfortunately progressed relentlessly toward

blindness. For example, when patients were being treated with ganciclovir, median time to progression was 2 months. When patients were treated with intravenous foscarnet, median progression time was 4 months. The most effective treatment was intravitreal ganciclovir implant, increasing the time to progression to 7 months. Immune recovery has allowed for CMV patients to be taken off of maintenance therapy [45–47]. Reactivation can occur, especially if patients CD4+ counts fall back below 50 cells/uL [47]. It appears that the CD4+ count is the best predictor of an effective immune response against CMV. Other laboratory values including HIV viral load and CMV culture data have not been correlated with a particular outcome. One area of active research is the correlation between CMV viral load and CMV-specific CDR T-cell response with the ability to promote an effective host immune response.

The widespread use of HAART has been attributed to an over 50% decrease in the number of new cases of CMV retinitis. A large retrospective review of over 1,200 HIV patients who had at least one CD4+ count below 100 cells/uL revealed a decrease in the incidence of three major opportunistic infections including CMV from 22 per 100 person-years to 3.7 per 100 person-years when HAART was instituted [41, 48]. Another study found the incidence of new CMV retinitis in the HAART era to be 5.6/100 person-years [45–47].

CMV retinitis remains a major problem, however. Many HIV-infected individuals had CMV retinitis prior to the introduction of HAART and have suffered permanently impaired vision, specifically secondary to retinal detachments and scarring following clearance of the infection. There additionally continue to be new cases occurring in HAART-failure patients who have low CD4+ T-lymphocyte count, and there are patients who despite successful HAART therapy still contract CMV retinitis [49]. Finally, CMV retinitis is expected to rise as HIV resistance to antiretroviral drugs increases and as HIV-infected individuals remain poorly informed about the HIV or have limited access to healthcare information. In addition, there are non-CMV-related ocular complications for HIV patients which persist. For example, retinal hemorrheologic abnormalities are found despite use of HAART. The pattern is changed from what is found in severely immunodeficient individuals, however. Cotton-wool spots, a feature often seen in severely immunodeficient individuals, become rare after immune recovery. For this reason, factors other than blood flow are thought to contribute to the findings in these patients. The remodeling of the microvasculature is thought to be a possibility [50, 51].

HAART has allowed the management of CMV retinitis to shift from previous short-term treatment to the long-term management of what has become, for many individuals, a chronic disease. There has been a paradigm shift of treatment objectives from slowing of disease progression to long-term suppression of disease activity altogether. The guidelines for management of CMV after the introduction of HAART have been summarized by the International AIDS Society-USA [52].

Discontinuation of Anti-cytomegalovirus Treatment

Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. A decision to discontinue anti-CMV drugs usually is based on several factors: a sustained rise in CD4+ T-lymphocyte count, a drop in HIV viral load, duration of HAART that is sufficient to effect immune recovery, and inactivity of CMV retinitis lesions. The Center for Disease Control (CDC) has stated that patients receiving HAART should have CD4+ T-lymphocyte counts of more than 100–150 cells/μL for at least 3–6 months prior to discontinuation of anti-CMV therapy [53]. However, Macdonald and colleagues observed that most patients for whom discontinuation of anti-CMV drugs was successful had values that far exceeded those guidelines [54].

Some clinicians require the additional evidence that the HIV viral load has dropped to fewer than 200 copies/uL [55]. However, Macdonald and colleagues further noted that the value of HIV viral load as a criterion for discontinuation of anti-CMV drugs was unclear [54]. Others have subsequently reported patients who have sustained CMV inactivity without maintenance treatment

despite HIV viral loads of greater than 30,000 copies/mL [55]. Regardless, HIV viral load may be a useful marker for eventual reactivation.

Patient Follow-up

Following effective discontinuation of anti-CMV therapy, CMV retinitis may reactivate. Studies have estimated that the risk of recurrence is approximately 0.02 events/person-years [55, 56]. For this reason, continuous monitoring of affected patients is essential. Additionally, with each relapse, the time to the next reactivation decreases. Putative laboratory measures are CD4+ T-cell count, HIV viral load, and CMV serum antigen or DNA [49, 57, 58].

As a nonspecific measure of immune function, CD4+ T-lymphocyte count is the most commonly followed parameter. While impaired CMV immunity is usually reflected in low CD4+ T-lymphocyte counts, some cases do not follow this rule, with development of CMV retinitis despite an adequate CD4 count. A number of studies have demonstrated a selective impairment of immune reactions against CMV present in patients with AIDS and CMV retinitis. Although tests of CMV immunity may provide an increased understanding of CMV retinitis in this setting, they are not yet commercially available and their ability to predict development or reactivation of CMV retinitis has not yet been demonstrated. For example, Sinclair and associates have shown that cytokine response of CD4+ T lymphocytes and CD8+ T lymphocytes to CMV antigen, as well as characteristics of CD8+ T-lymphocyte profiles, differs between patients receiving HAART who have prolonged inactivity of CMV retinitis and those with active infections [59].

Serial ophthalmic examinations and patient education regarding symptoms of CMV retinitis are additional components of effective screening programs. Because patients who are "at risk" may develop CMV and suffer substantial visual impairment within a 6-month time frame, it is critical to educate at-risk individuals about the symptoms of CMV retinitis and necessity of timely follow-up. With an increasing percentage of asymptomatic patients in the HAART era, the need for rigorous screening programs is growing, as even small peripheral lesions can progress quickly without treatment and result in visual disturbance. Because CMV retinitis occurs in immunocompromised individuals, treatment of underlying disease is the most important prevention of retinitis. Untreated retinitis will progress to blindness from retinal necrosis, optic nerve involvement, or retinal detachment. It is also important to note that retinitis can relapse despite ongoing treatment. Reinduction, a change in medication, combination drug therapy, or an ocular implant are alternatives for management.

Acquired Immunodeficiency Syndrome (AIDS)

The first era in the study of ocular HIV was a short period of rapid discovery, in which the spectrum of ophthalmic disorders associated with AIDS was identified. Most of these disorders had been identified prior to the epidemic; however, they were quite rare before the rise of HIV and AIDS. Examples of this phenomenon include the increased prevalence of Kaposi sarcoma, progressive outer retinal necrosis (PORN), and choroidal pneumocystosis. Kaposi sarcoma, for example, is associated with infection of human herpes virus 8 and has become the most common AIDS-associated eyelid and conjunctival tumor [60]. PORN is a unique variant of herpetic retinitis only seen in immunocompromised patients (Fig. 8.7a, b) [61].

HIV

HIV-1 is a lentivirus. As a retrovirus, it has only RNA in its genome and relies on reverse transcriptase for its replication. HIV-1 was initially discovered and termed LAV (lymphotropic adenovirus). Relative to HIV-2, which has been identified primarily in western Africa, HIV-1 is more virulent, is more infective, and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 compared to

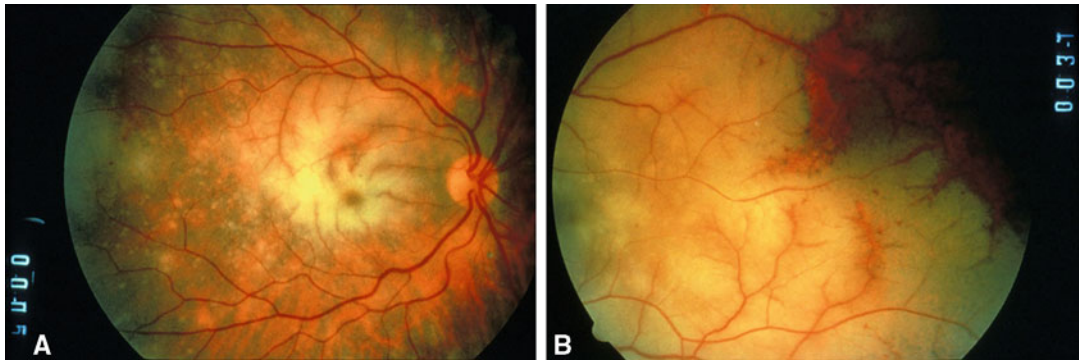

Fig. 8.7 Progressive outer retinal necrosis occurs in a severely immunosuppressed patient is notable for sparing of the inner retinal circulation and lack of associated vitritis (**a**). Typical perivascular clearing in PORN (**b**)

HIV-1 implies that fewer of those exposed to HIV-2 will be infected per exposure. HIV has predilection for infecting CD4+ T lymphocytes, a cell type that is crucial for proper immune response. As HIV infection propagates, the CD4+ T cells lyse and the host experiences a severe immunosuppression.

Epidemiology

As of 2007, the prevalence of HIV has been documented at over one million people in the United States and 33 million people worldwide [62]. In 2005 alone, there were more than 40,000 new cases of AIDS in the United States reported to the CDC. The demographics of the AIDS epidemic have changed in the United States over the past 25 years. HIV is predominantly spread through sexual transmission. Homosexual activity was responsible for most transmission until the mid-1990s, but now, heterosexual activity accounts for the major route of transmission in developed countries. Intravenous drug abuse is another common route of disease transmission. Women now account for one quarter of HIV infections. Transmission from mother to child may occur prenatally, during parturition, or postnatally during breast feeding. Professional healthcare workers are also at risk for hematogenous transmission via needlestick injury. Seroconversion for this incident is about 0.3%, which is nearly 100 times less than that for hepatitis C or hepatitis B [63].

Diagnosis

HIV infection can be detected by the presence of antibody to viral antigens by ELISA, 2–8 weeks following inoculation, and diagnosis is confirmed by Western blot for gag, pol, and env proteins. Immunoassays for HIV detection perform better than other serological assays, and most short comings are related to user error [64]. ELISA tests are 100% sensitive, although there are rare false-positive results. The HIV virus has been identified in the cornea, vitreous, and retina.

HIV Disease

There is an acute retroviral syndrome which occurs 1–6 weeks following inoculation. This consists of fever, rash, myalgias, headache, and/or gastrointestinal symptoms. The CD4+ count is reduced and, unless treatment is initiated, the count continues to reduce by approximately 75 cells/uL/year [63]. Individuals with HIV loads greater than 30,000 copies/mL have an 80% likelihood of developing AIDS within 6 years, whereas individuals with 500 copies/mL have a 5% likelihood. Typically, AIDS develops 10 years following initial HIV exposure and infection and generally occurs when the CD4+ count falls below 200 cells/uL. It is at this point that opportunistic infections may occur, most notably Pneumocystis carinii, Cryptococcus neoformans, and Cytomegalovirus. Susceptibility to the

various opportunistic infections occurs at different CD4+ count thresholds, with *P. carinii* occurrence below 200 cells/uL and CMV occurrence below 50 cells/uL.

HIV Therapy

The rate of the decline in CD4+ count and rise of HIV viral load are two important factors in determining treatment plans. There are differing opinions on the process, but one general rule focuses on treatment initiation for all patients in whom CD4+ count falls below 350 cells/uL. When therapy is started, a HAART regimen is used, consisting of one protease inhibitor and two nucleoside inhibitors. Lack of compliance on the part of the patient can lead to failure of therapy secondary to rapid development of resistance.

Ocular Manifestations of HIV

While HIV may be isolated from every layer of the eye, clinically relevant ocular manifestations are limited to the posterior segment. HIV-associated microvasculopathy, for example, causes retinal nerve fiber layer infarcts observed as cotton-wool spots (Fig. 8.8). The incidence of these superficial white fluffy infarcts increases with the degree of immunosuppression, secondary to an underlying microvasculopathy likely associated with increasing immune complex formation [65].

Progressive Outer Retinal Necrosis

Initially described in immunocompromised patients, progressive outer retinal necrosis (PORN) is a rapidly progressive syndrome. Although both are caused by herpesviruses, PORN may be differentiated from ARN based on its distinctive clinical appearance with the absence of vitreous inflammation. Secondary to its high incidence of retinal detachment as well as affinity for bilateral involvement, PORN carries a very poor prognosis.

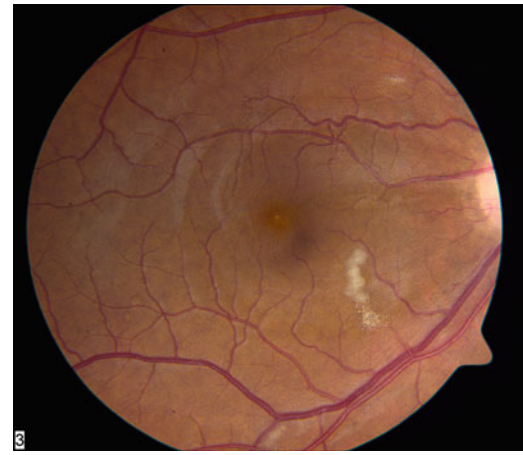

Fig. 8.8 Cotton-wool spots in HIV retinopathy

Diagnosis

PORN syndrome was originally described in two HIV patients and is thought to be a variant of ARN in a immunocompromised host [66]. Margolis described a similar syndrome in VZV patients with AIDS and also noted a rapidly progressing relentless necrotizing retinitis [67]. While PORN commonly occurs in association with cutaneous zoster infection or zoster ophthalmicus, it may occur in the absence of these disease entities as well. Macular lesions were noted in 21 of the 65 eyes in another study, with multifocal deep retinal lesions typically found in the periphery [68]. Most patients were unilaterally affected by these macular lesions, but 25% demonstrated peripheral disruption in the other eye. In addition, asymptomatic disease was noted in 11% of the 65 eyes. The lesions rapidly progress to confluence, and although the syndrome is described as involving the outer retina, pathologic examination suggests that the disease can lead to significant destruction of the inner retina [66].

The differential diagnosis for PORN is similar to that of ARN, but it is important to differentiate between the two infections. Unlike typical ARN, there is little or no vasculitis, less vitritis, and early posterior pole involvement and bilateral disease is more common. Furthermore, the retinal lesions in PORN involve in the deep retinal tissue, whereas full-thickness involvement predominates

in ARN. The lesions are nearly uncontrollable in PORN and often progress to confluence.

Etiology

Varicella-zoster virus and herpes simplex virus have been implicated in the cause of PORN. Most patients with PORN have impaired immune status [69]. In one study, the median CD4+ T-cell count was 21 cells/uL [66].

Therapy

PORN is associated with an extremely poor prognosis despite vigorous treatment protocols. As in ARN, combinations of intravitreal and intravenous ganciclovir and foscarnet may be used. Unlike ARN, though, these medications appear to be more effective than intravenous acyclovir.

Retinitis/Choroiditis Following Other Systemic Illnesses

Measles: Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a subacute encephalopathy affecting unvaccinated children and young adolescents arising approximately 6–8 years following primary infection. It infrequently affects adults and pregnant women. SSPE is caused by an aberrant measles virus, known as the SSPE virus, which differs from wild-type measles viruses by several mutations in the matrix gene. The characteristic clinical manifestations of SSPE include visual impairment, behavioral changes, cognitive decline, myoclonic jerks progressing to spastic paresis, seizures, bilateral pyramidal signs, dementia, coma, and death [70].

Visual impairment occurs in up to 50% of patients secondary to maculopathy with focal retinitis and RPE changes, involvement of the optic nerve with papilledema or disc pallor, or visual cortex damage leading to cortical blindness [71]. Additional ocular manifestations include nystagmus, gaze palsies, and ptosis. These symptoms may precede the neurologic manifestations by a several weeks up to 2 years [72–74]. It has been suggested that measles virus–acquired virulent neurotropism develops in the retina before involvement of the central nervous system [75]. Ultrastructural examination of the retina in an affected patient demonstrated numerous filamentous microtubular intranuclear viral inclusions consistent with the measles virus in the retinal nuclear layers [76]. While diagnosis is made based on this unique constellation of clinical manifestations, it is important to consider the diagnosis of SSPE in cases with acute vision loss resulting from cortical blindness even when other classical findings of SSPE are absent [77]. Further diagnostic clues can be given by periodic electroencephalographic discharges, identification of raised anti-measles IgG antibody in the serum or cerebrospinal fluid, or by the observation of panencephalitis with histopathology as described above on brain biopsy.

At present, there is no effective treatment for SSPE. Oral isoprinosine and intrathecal or intraventricular alpha-interferon may prolong survival to some extent. Immunization against measles is currently the most effective strategy against SSPE.

Rubella

Rubella infection is caused by a highly contagious virus of the Togaviridae family. It is a single-stranded RNA virus that is surrounded by a lipid envelope. German measles, or acquired infection, is associated with mild systemic symptoms in adults and children. The most frequent ocular finding is conjunctivitis, although keratitis and retinitis may infrequently occur [78]. The retinitis resolves spontaneously with return to normal vision.

Unlike acquired infection, congenital rubella is a devastating syndrome. It occurs when virus crosses the placenta during maternal viremia approximately 10–12 days following primary infection [79]. The frequency and severity of congenital infection is related to gestational age at the onset of maternal infection. The risk is

greatest, reported at 81–100%, when maternal infection occurs during the first trimester or in the final month of pregnancy [80].

As a result of immunization programs instituted in the United States in 1969, congenital rubella is rare. Five to twenty-five percent of women of child-bearing age in the United States lack rubella-specific antibodies and are susceptible to infection [80]. Congenital rubella syndrome presents with a chronic infection beginning in the neonatal period and continuing through infancy. The most common systemic manifestation of congenital rubella syndrome is hearing loss [81]. Cardiac malformations have been reported in 67–69% of infected patients [82]. Systemic manifestations include thrombocytopenia, hepatosplenomegaly, low birth weight, failure to thrive, psychomotor and mental retardation, and microcephaly [83].

Ocular manifestations occur in 30–78% of infants and children, most commonly chorioretinitis (25–50%), followed by cataract (15%) and glaucoma (10%) [79, 82]. Chorioretinitis leads to a classic rubella retinopathy consisting of salt-and-pepper pigmentary changes with a mottled, blotchy, irregular pigmentation, usually deep to normal retinal vasculature. The foveal reflex is usually absent, and the optic nerve may be pale. The condition may occur focally in only one quadrant or unilaterally and may be stationary or progressive after birth [84]. Despite these abnormalities, vision is usually normal or minimally affected by rubella retinopathy. However, rubella proliferation at the level of the RPE leads to RPE atrophy and rarely subsequent choroidal neovascular membrane formation, resulting in a significant decline in visual acuity [85].

Because maternal infection is often subclinical, the diagnosis of congenital rubella is suspected based on the observation of associated congenital anomalies. Diagnosis is confirmed by a fourfold increase in rubella-specific IgG in paired sera 2 weeks apart or the new appearance of rubella-specific IgM in the neonate [86].

The most effective treatment is prevention of maternal rubella infection with immunization programs. There is no specific antiviral therapy of either acquired or congenital rubella infection, and treatment is supportive. While rubella retinopathy does not require treatment, the rare complication of choroidal neovascularization may require photocoagulation, photodynamic therapy, or anti-angiogenic treatment. Rubella retinitis with acquired infection or postvaccination optic neuritis may respond to systemic steroids.

West Nile Virus

West Nile virus (WNV) was first isolated in 1937 in the West Nile district of Uganda. Later, in 1957, it was recognized as a cause of meningoencephalitis during an outbreak in an Israeli nursing home. Since then, several outbreaks have been reported worldwide, including a Canadian epidemic which extended to five provinces [87–91]. The first reported human WNV infection in the United States was in 1999 during an outbreak of meningoencephalitis in New York City [92]. It has subsequently spread throughout the country.

WNV is transmitted to humans through the bite of an infected Culex mosquito. The mosquito acquires the virus through feeding on infected birds, which typically are the natural host of the virus and have a high-level viremia. Crows and blue jays of the family Corvidae are particularly susceptible to infections with WNV. Corresponding to the mosquito season, the majority of human infections occur in August and September [93].

There are three clinical categories of systemic WNV infection: (1) asymptomatic, (2) West Nile fever, and (3) West Nile meningoencephalitis. Most individuals remain asymptomatic with only 20% of patients developing symptoms and only 1 in 150 infected patients developing meningoencephalitis [94]. Clinical features of WNV fever include sudden onset of high-grade fever, headache, myalgias, gastrointestinal symptoms, pharyngitis, arthralgias, fatigue, and maculopapular rash on the chest, back, and lower extremities. Following an incubation period ranging between 2 and 14 days, the acute illness is self-limiting, typically lasting less than a week [95]. Presenting

ocular complaints include ocular pain, photophobia, conjunctival injection, and blurred vision. Garg and Jampol have identified five categories of intraocular manifestations of WNV infection [94]: (1) multifocal chorioretinitis with lesions either widely scattered or in linear arrays, (2) uveitis without focal lesions, (3) occlusive retinal vasculitis, (4) congenital chorioretinal scarring secondary to intrauterine transmission, and (5) optic neuritis.

WNV chorioretinitis most commonly presents with associated uveitis, and although most of the patients have uveitis in association with chorioretinitis, Kuchtey et al. described a patient with vitritis and iritis in the absence of chorioretinitis [96]. Acuity on presentation ranges from 20/25 to counting fingers vision and most cases demonstrate bilateral involvement. The chorioretinal lesions during the active phase are deep, flat, and whitish yellow in color, ranging from 200 to 1,000 μm in diameter. The lesions soon become pigmented, sometimes as early as 2 weeks after initial presentation. Fluorescein angiography demonstrates hyperfluorescent lesions which display late leakage when active and late staining when inactive or quiescent. Usually, inflammation resolves and vision returns to near baseline within several months. However, there have been rare reports of development of choroidal neovascular membrane underlying a WNV chorioretinal scar [97–100].

Three cases of bilateral optic neuritis have been reported in association with WNV meningoencephalitis [70]. However, although all three patients had lumbar punctures performed, opening pressures were not reported. Thus, increased intracranial pressure may have been responsible for the observed bilateral optic nerve swelling associated with papilledema [101–103].

There is currently no proven treatment for WNV infection. It usually follows a self-limiting disease course. However, concurrent diabetes mellitus has been linked to WNV-associated death. When needed, therapy is supportive, with hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. The mainstay of WNV infection control is prevention. Public health measures to reduce the number of mosquitoes include draining water from breeding sites and use of mosquito larvicides or methoprene, a mosquito-maturation inhibitor. Antiviral agents such as ribavirin and interferon-2B, although effective in vitro, were found clinically ineffective [104]. Vaccination, a long-term solution, is still in the research phase [105].

Other Systemic Illnesses

There are several additional viral infections suspected to cause choroiditis. For example, the influenza virus has been implicated in the etiology of acute posterior multifocal placoid pigment epitheliopathy (APMPPE). This disorder is usually diagnosed in young patients following a prodromal viral illness. Azar and colleagues demonstrated adenoviral infection in one patient [106]. The average age of onset is 20–50 years and presents with rapid visual loss in one or both eyes. The characteristic findings include the presence of creamy, yellow-white lesions at the level of the RPE with sparing of the retina. The lesions are circumscribed and discreet, frequently coalescing to large confluent areas that typically fade within weeks to become hypo-/hyperpigmented. Gass initially described this entity in 1968 [107]. Visual acuity is better than 20/30 in >90% of affected eyes. The diagnosis is confirmed by the characteristic angiographic finding of early blockage and late staining which strongly suggests that the choriocapillaris is the primary site of infection.

Controversies and Perspectives

What Is the Best Method of Providing Rapid and Specific Treatment for Infectious Retinitis?

PCR studies should be obtained from vitreous aspirates when a patient presents with a rapidly progressive necrotizing retinitis, but treatment should not await laboratory confirmation. Traditional treatment for ARN consists of induction therapy with

intravenous acyclovir for 7–10 days followed by oral antiviral medications for approximately 3 months. Newer intravitreal and oral antiviral regimens have emerged over the past decade, but a recent analysis of current treatment practices at four tertiary eye care centers identified no single treatment strategy as the standard of care for ARN. Fortunately, the variation in initial antiviral strategy did not affect final outcome, suggesting that the physician may use his or her own judgment on the basis of available resources.

The same study also revealed variation in long-term oral antiviral treatment strategies. Treatment duration varied greatly, ranging from 1.5 to 75.7 months, and usually consisted of valacyclovir. Unfortunately, the ideal duration and relative efficacy of these long-term oral antiviral regimens remain unclear, and the visual outcome was generally poor [43].

When Should Patients' CMV Antiviral Treatment Be Discontinued After Onset of Immune Recovery Uveitis?

Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. A decision to discontinue anti-CMV drugs usually is based on several factors: a sustained rise in CD4+ T-lymphocyte count, a drop in HIV viral load, duration of HAART that is sufficient to effect immune recovery, and inactivity of CMV retinitis lesions. The Centers for Disease Control (CDC) has stated that patients receiving HAART should have CD4+ T-lymphocyte counts of more than 100–150 cells/μL for at least 3–6 months prior to discontinuation of anti-CMV therapy [53].

What Is the Best Surgical Approach for Repair of Secondary Retinal Detachment?

The basic principle of viral-associated retinal detachment repair is to elevate the posterior hyaloid and remove vitreous as completely as possible. It is often not prudent to be aggressive with the hyaloid in areas of necrosis as this induces more retinal tears. In these areas, a close shave of vitreous is effective. Laser is applied in confluent burns in the area of necrosis with overlap onto healthy retina. A scleral buckle may or not be necessary and is used to protect healthy retina from tearing. A buckle is often not helpful when retinal necrosis extends too posteriorly to be supported, and therefore, the buckle can help protect uninvolved retina. Patients can be left phakic or pseudophakic. Finally, the choice of vitreous tamponade can either be silicone oil or C3F8. The previous use of silicone only reflected the fact that most patients with CMV secondary to HIV perished within 6 months of CMV detachment, but HAART has dramatically changed this finding. C3F8 works equally as well as silicone, even in cases with multiple necrotic holes. Finally, a Vitrasert® is a nice adjunct to herpes-related detachment and can be used with gas or silicone oil.

What Causes Reactivation of HSV in Retinal Tissue?

Although primary infection with HSV can involve ocular and adnexal sites and can manifest as blepharitis, conjunctivitis, or corneal epithelial keratitis, it is not known precisely why secondary ocular HSV retinal infection occurs after latency is established within the central nervous system. The latent infection occurs in the trigeminal ganglia and can remain latent during the lifetime of the host. One observation is that during latency, there is abundant transcription at the region encoding the latency-associated transcript, which may play significant roles in the maintenance of latency as well as neuronal reactivation. Many host and viral factors have been implicated in HSV reactivation from latency. Additionally, HSV DNA is shed into tears and saliva of most adults, but in most cases, this does not result in lesions. Finally, recurrent disease occurs as HSV is carried by anterograde transport to the original site of infection, or any other site innervated by the latently infected ganglia and can reinfect the ocular tissues [108].

Focal Points

Viral infections of the retina and choroid are rare but important causes of visual loss. The nearly uniform involvement of choroidal and retinal vessels demonstrates the likely hematogenous spread of systemic viral infection to the eye. The retina provides a good substrate for viral infection because of its relatively immunoprivileged status and its connection to the central nervous system where latent virus can become activated. The principles of management of viral-associated retinitis are:

1. Prompt diagnosis
2. Immediate intraocular and then systemic (intravenous or oral) treatment
3. Close surveillance at weekly intervals early to see treatment effect in at least 2 weeks followed by monthly intervals late for progression to retinal detachment
4. Systemic evaluation for presence of immunosuppression
5. Close inspection of the companion eye

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