Viral Retinitis

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Introduction

Herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) are among the most common viral pathogens responsible for infectious retinitis. These viruses can cause chronic anterior uveitis, acute retinal necrosis (ARN), and progressive outer retinal necrosis (PORN), the latter two being responsible in some cases for sequelae such as optic neuropathy, chronic retinal ischemia and retinal detachment. ARN is classically found in immunocompetent patients, whereas PORN is most common in immunocompromised patients, initially coming to light during the human immunodeficiency virus (HIV)-associated acquired immunodeficiency syndrome (AIDS) epidemic.

CMV affects roughly 45% to 100% of the population depending on geography [1]. HSV-1 subtype has been identified in between 45% and 98% of the world population, whereas 40–63% of the United States (US) population has been shown to have antibodies against this virus [2]. Seropositivity increases with age, as expected. It has been shown that lower income and minority groups also have a higher seropositive rate for HSV-1 in the United States [2]. HSV-2 tends to affect fewer people, with 20–25% of the US population having antibodies by 40 years of age [2]. Classically, HSV-1 has been associated with oral HSV lesions and HSV-2 more so with genital lesions; however, this distinction is beginning to blur.

CMV retinitis continues to be problematic especially in hematopoietic stem cell transplant (HSCT) recipients and less so in solid organ transplant (SOT) recipients. Increased levels of immunosuppressive medications pose a clinical challenge for viral reactivation. However, advances in antiviral therapy have offset this risk with preemptive and prophylactic strategies in transplant recipients.

Other viruses that have been implicated to cause ocular infections include chikungunya virus, dengue virus, yellow fever virus (YFV), West Nile virus (WNV), and Zika virus (ZV) [3–5]. WNV is a single-stranded RNA flavivirus which is transmitted by the *Culex* genus of mosquitoes and has been identified in Africa, Europe, Australia, Asia, the United States, Canada, Mexico, Central America, and South America [3]. Patients may develop chorioretinitis, which is associated with concomitant neurologic disease

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such as encephalitis. Chikungunya, dengue, and Zika viruses are all arboviruses transmitted by the *Aedes aegypti* mosquito and occasionally other *Aedes* species. Chikungunya virus is an alphavirus, while dengue and Zika viruses belong to the *Flaviviridae* family. These are all single-stranded RNA viruses. Retinitis is less common with these viruses as less than 10% of symptomatic dengue infections have been identified to have ocular manifestations, whereas chikungunya and Zika infections have an even lower prevalence of ocular disease, with only a few cases reported. Treatment of these viruses is limited as there are no active antiviral medications, and symptoms are managed with corticosteroids [3–5].

Pathogenesis

HSV and VZV are neurotropic viruses which cause latent infection by integrating viral genomic material into the host tissue [6]. Chronic latency is then interrupted by periodic reactivation to a variety of internal and external triggers [2]. Patients tend to develop a primary HSV infection of mucocutaneous surfaces from which the virus integrates into the nerve ganglion and remains latent for life. In contrast, VZV primary infection manifests as chickenpox; however, the incidence of this is decreasing significantly due to vaccination campaigns [7]. The predominant theory of the pathogenesis of herpes virus infection is a latent infection in the dorsal root ganglia or trigeminal ganglion with reactivation in specific dermatomes with retrograde movement of the virus [6]. Reactivation has been associated with stressors such as sunlight, trauma, emotional stress, menstruation, or other infections [8]. There has also been suggestion that HSV can remain dormant in corneal nerves after prior keratitis, as it is an immunologically privileged site [9].

Entry of HSV into ocular cells can occur by exogenous exposure to the virus (such as via corneal transplant), local reactivation in the cornea, or reactivated virus that travels anterograde along the ophthalmic division of the trigeminal nerve [9]. Interactions between the nectin-1 receptor and the viral surface glycoprotein gD facilitate endocytosis of HSV-1, 2 into a variety of ocular cell types including retinal pigment epithelial cells and are thought to be the primary mechanism of viral entry [10].

CMV retinitis was described in patients with HIV infection in the early 1980s [11]. It occurred late in the disease course when the CD4+ T-lymphocyte count dropped below 50 cells per microliter. CMV retinitis also occurs in immunocompromised patients such as HSCT recipients [12, 13]. It has also been described in immunocompetent individuals, but this seems to be a much rarer occurrence. The pathogenesis is similar to HSV or VZV, in that it is thought to be reactivation of latent virus that causes the disease. Roughly 56% of Australians between 1 and 59 years of age were found to be seropositive for CMV in a 2006 study [14]. Other than in advanced HIV infection, CMV retinitis has been described in organ transplant recipients. An example of such a case occurred in a deceased donor kidney transplant recipient who had received belatacept [15]. The patient had several episodes of CMV reactivation treated systemically and then developed a multidrug-resistant CMV retinitis with the virus detected in plasma and aqueous humor.

In HSCT recipients, risk of CMV retinitis is determined by recipient CMV IgG status. If the recipient is CMV IgG-positive, denoting the presence of latent CMV infection, there is risk for reactivation. If a CMV IgG-positive recipient receives a HSCT from a CMV IgG-negative donor, the newly acquired immune system will be CMV-naïve putting the recipient at risk for CMV reactivation [16]. The induction and conditioning regimen, which often includes high-dose corticosteroids, T-cell-depleting agents, and treatment for graft-versus-host disease in allogeneic HSCT recipients, may also play a role in patient reactivation [16]. Valganciclovir and letermovir are currently approved for CMV prophylaxis in high-risk groups. Failure of prophylaxis may occur due to inadequate medication adherence, dosing inconsistency, or prophylaxis discontinuation in response to adverse effects of medications (such as pancytopenia). CMV retinitis develops in 11.3% of SOT recipients with CMV viremia [17]. Risk factors for poor progno-

sis included concurrent systemic CMV disease and foveal involvement in one study. In this study, prevalence of CMV retinitis trended towards lower rates in SOT recipients (8.7%) than HSCT recipients (15.4%), with a p value of 0.052. The mortality rate over the mean 11.7-month follow-up in patients diagnosed with CMV retinitis was 52.4% in HSCT recipients compared to 5.6% in SOT recipients ($p < 0.001$) [17].

In cases of CMV or disseminated herpesvirus infection, the virus enters the eye hematogenously through a compromised blood-retinal barrier [18]. Retinal microvascular endothelial cells are the initial target of CMV infection, and from there CMV spreads to adjacent perivascular glia, Muller cells, and other retinal cells such as the retinal pigment epithelium [18]. The virus infects retinal pigment epithelial cells via their apical membrane and spreads laterally cell-to-cell [19]. In response to viral exposure, infected endothelial cells undergo apoptosis and stimulate the release of pro-inflammatory mediators by neurosensory and glial cells [18]. Tumor necrosis factor-alpha and **interferon-gamma** sensitize the retinal pigment epithelial cells and other retinal cells to undergo FasL-mediated apoptosis [20]. EBV has also been implicated in viral retinitis, though there are only a handful of reported cases with molecular confirmation.

In immunocompetent individuals, the presence of virus in the eye provokes a strong immunologic response from the host, causing infiltration of the vitreous and retina by mononuclear cells. A high proportion of T lymphocytes, particularly CD4+ T cells (70%), were isolated from vitreous sample with acute retinal necrosis [21]. Retinal arteriolar vasculitis results in vascular occlusion and necrosis of downstream retinal tissue.

In contrast to the above infections, the majority of arbovirus-mediated retinitis occurs during the acute infectious phase. Dengue virus has four separate serotypes and typically causes a self-limited flu-like syndrome. However it can manifest as the feared dengue hemorrhagic fever with severe bleeding, respiratory distress, and multiorgan failure, which is more common with repeated infection with a different serotype [3]. Retinitis most commonly manifests within 5–7 days of the initial infection and is thought to be due to an immune-mediated response to the virus. In young adults, ocular manifestations tend to occur at the nadir of thrombocytopenia, the latter of which may be explained by circulatory compromise or immune complex deposition [3].

West Nile-associated retinitis can be seen as commonly as 80% in patients with concomitant neurologic disease [3, 5]. Neurologic complications occur in less than 1% of WN virus infections, however. The pathogenesis is likely due to direct infection and is characterized as multifocal chorioretinitis. Vascular manifestations can occur with retinal hemorrhages, retinal vascular sheathing, vascular leakage, and possibly occlusive retinal vasculitis [3–5].

Chikungunya virus infections typically manifest as fevers, malaise, arthralgia, rash, vomiting, and myalgias, but meningoencephalitis has also been reported [4]. Ocular manifestations can be unilateral or bilateral, and the pathogenesis is unknown. Ocular infections occur concomitantly with systemic disease, so there may be a component of direct infection or immunologic response to the virus driving the ocular manifestations [4].

Zika virus infection manifests as fever, conjunctivitis, and rash and can result in severe birth defects such as microcephaly if primary infection occurs during pregnancy [3]. Macular atrophy from in utero infections has been reported. Acute maculopathy, multifocal choroiditis, and optic neuritis have also been reported in adults [3]. Zika virus has been demonstrated to directly infect multiple retinal cell types and induce apoptosis in animal models.

Clinical Features

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) describe two patterns that exist along a spectrum of viral necrotizing retinitis. ARN is characterized by multifocal, well-demarcated, peripheral retinal whitening that rapidly coalesces and spreads in a circumferential pattern [22]. It is frequently accompanied

by anterior chamber inflammation, occlusive arteriolitis, and prominent vitritis [22]. Concurrent optic nerve involvement can also be seen and can be visually devastating.

HSV encephalitis and acute retinal necrosis may occur concomitantly [23]. Patients may present with new-onset seizures, fevers, or altered mental status, and these features may prompt further work up for encephalitis or meningitis. Often, oral lesions are not associated with concomitant HSV meningitis, encephalitis, or retinitis. The disease presentation is frequently insidious with no prior warning or prodrome.

In PORN, retinal necrosis begins in the outer retina but quickly progresses to full-thickness involvement. In contrast to ARN, the multifocal retinal whitening tends to begin more posteriorly, and there is a relative absence or reduced degree of inflammation in the rest of the eye due to the profound immunosuppression of the host. A characteristic "cracked mud" appearance has been described in PORN owing to a perivascular pattern of retinal sparing, which can be present until late stages of PORN. Angiographic studies have demonstrated sparing of the perivenous capillary network despite concurrent arteriolar attenuation and retinal staining in eyes with diffuse retinal involvement [24].

After resolution of active retinitis, the eye enters the cicatricial phase. Retinal holes or breaks frequently occur at the junction of normal and atrophic retina. Additionally, proliferative vitreoretinopathy develops as a later consequence of the acute immunologic response. Retinal detachment is common, occurring by a combination of rhegmatogenous and tractional mechanisms.

Notably, VZV infection is associated with more aggressive disease and poorer visual outcomes in patients with acute retinal necrosis [25]. Compared to HSV ARN, a lower proportion of patients with VZV ARN presented with good visual acuity (≥20/60), and a higher portion had poor vision (≤20/200) at 1 year. This difference in visual outcome may be mediated by a higher rate of retinal detachment in eyes with VZV ARN [25].

CMV infections may present with a multitude of organ systems involved including pneumonitis, colitis, enteritis, pancreatitis, gastritis, pancytopenia, myocarditis, meningitis, and nephritis [14]. Primary infection most commonly presents as an acute mononucleosis. Retinitis has not been reported in acute infections. CMV retinitis classically presents as one of three pathologic patterns. The "frosted branch angiitis" pattern is characterized by prominent peri-arteriolar sheathing. In the hemorrhagic pattern, retinal hemorrhages and yellow-white necrotic lesions are found, frequently perivascularly. The granular form involves peripheral retinal granularity with minimal frank hemorrhage or necrosis. Compared to ARN and PORN, there is relatively reduced or absent intraocular inflammation due to the underlying immunocompromised status of the host, and the retinitis is typically slower to progress. Consequently, patients with CMV retinitis may sometimes suffer from delayed diagnosis due to fewer or more subtle symptoms, with up to 33% of CMV retinitis patients reporting no symptoms in one case series [24].

Lab Testing

The differential diagnosis of infectious retinitis includes *Toxoplasma gondii*, CMV, HSV, VZV, *Mycobacterium tuberculosis*, and *Treponema pallidum.* If appropriate risk factors are present, such as travel to a known endemic area or a high-volume season for mosquito bites, PCR and antibody testing can be performed for West Nile, dengue, chikungunya, and Zika viruses. Some of these can only be completed by special laboratories or the Centers for Disease Control and Prevention (CDC). Laboratory analysis should be done with the aim of ruling out these causes when possible and should include HIV screen, treponemal and non-treponemal syphilis screens, latent tuberculosis screening through an interferon-gamma release (QuantiFERON) assay, and *T. gondii* serum IgG screen. Brain imaging and cerebrospinal fluid (CSF) analysis should be considered on a case-by-case basis, as encephalitis or meningitis can also present concomitantly with retinitis [26].

Serum CMV levels appear to have limited utility in diagnosing CMV retinitis as they are not sen-

sitive [13]. The same is true of HSV and VZV serology. Although viral retinitis is a clinical diagnosis, molecular confirmation is helpful to determine the etiologic virus and to differentiate from masqueraders such as toxoplasmosis in immunocompromised individuals. Polymerase chain reaction (PCR) testing is the gold standard to confirm the intraocular presence of HSV, VZV, or CMV. An aqueous humor sample is ideal for PCR testing. PCR of an aqueous sample was able to identify HSV or VZV DNA in 79% to 100% of cases with necrotizing retinitis [27, 28]. Given the high sensitivity of PCR using aqueous samples, vitreous tap is not the preferred diagnostic procedure, especially given an increased risk of vitreous traction that may potentiate retinal tears or detachments in already weakened portions of the retina.

In addition to viral PCR, testing for other causes of retinitis should be obtained. Toxoplasmosis in immunocompromised patients can lead to a similar appearance, and therefore an aqueous sample can also be tested for toxoplasma PCR. However, empiric treatment for viral retinitis should not be delayed while awaiting laboratory testing, given the potential for significant and rapid visual morbidity.

Management

A combination of systemic and local therapy forms the mainstay of treatment. Therapy should be initiated at the time of clinical diagnosis and should not be delayed for molecular confirmation.

HSV and VZV Retinitis

The American Academy of Ophthalmology recommendations for antiviral treatment of ARN include systemic acyclovir, valacyclovir, famciclovir, foscarnet, or ganciclovir [27]. Initially, oral or intravenous antivirals can be used based on the preference or experience of the treating physician. A few studies have shown that oral antiviral agents can be effective in reducing progression to retinal detachment [29, 30]. One systematic review focused on retinal detachment after ARN and the efficacies of the published interventions. The conclusion from this study was VZV-associated ARN may require more intensive interventions as the incidence of retinal detachment was higher compared to HSV-associated ARN. Additionally, systemic antivirals are effective and prophylactic vitrectomy may provide benefit [31]. Zhao et al. reviewed retinal detachment in patients with viral retinitis for alternative or additional treatment options but did not evaluate oral versus intravenous antiviral treatment.

Intravitreal concentrations of valacyclovir attain inhibitory concentrations against VZV, HSV-1, and HSV-2 [32]. The ocular penetration of valacyclovir is up to 25% of serum concentration [32] and achieves the reported inhibitory ranges for drug level for inhibition of VZV, HSV-1, and HSV-2. Simulation models demonstrate that high-dose valacyclovir reaches comparable vitreous drug concentration as intravenous acyclovir [33]. Valacyclovir is preferred over oral acyclovir due to its superior pharmacokinetic characteristics. It has excellent bioavailability of up to 54.2% [34]. Oral valacyclovir achieves three to five times higher plasma levels than oral acyclovir. (Weller). In patients who are unreliable with medication compliance, or present with bilateral viral retinitis, hospital admission for intravenous antivirals is reasonable. In contrast, oral acyclovir does not demonstrate the vitreous penetration that its prodrug valacyclovir can achieve. PORN generally requires higher doses of antiviral medication and has a worse prognosis [35]. This is usually managed with systemic antivirals plus intravitreal injections. Valacyclovir is dosed at 500 mg three times daily for HSV and 1 g three times daily for VZV, although many specialists will use the 1 gram dose for extensive retinal necrosis regardless of etiologic virus to attain high vitreous concentration of antiviral. Given the potential for rapid vision decline, some specialists recommend an initial dose of 2 g three times daily for at least 3 weeks or until areas of retinitis begin to pigment at the edges. Subsequently, valacyclovir dosing can be reduced to 1 g daily for maintenance, with most practitioners recommending

lifetime prophylaxis to prevent reactivation or involvement of the fellow eye.

Important adverse effects of systemic antivirals include thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and nephrotoxicity, so its use is contraindicated with patients with certain pre-existing hematologic abnormalities. Baseline comprehensive metabolic panel should be obtained prior to or at the time of medication initiation, as dose adjustments should be made based on renal function.

Adjunctive therapy with intravitreal foscarnet has been shown to reduce the risk of retinal detachment compared to systemic therapy alone [25, 36]. Patients receiving combination therapy instead of systemic therapy alone were also more likely to gain two or more lines of visual acuity [36]. Additionally, intravitreal therapy represents an important treatment modality in situations in which there are contraindications to or dosing restrictions of systemic treatment, most commonly related to acute or chronic renal dysfunction.

Acyclovir resistance in HSV has an incidence of roughly 0.1–0.7% [35]. Such resistance in VZV is significantly lower but not well defined. Acyclovir resistance is mediated by mutations in viral thymidine kinase which inhibits phosphorylation of the antiviral into its active form. The common genes associated with this are UL23 in HSV or ORF36 in VZV. Resistance should be suspected in patients who have been on long-term suppressive therapy and present with a breakthrough infection or fail to respond in a reasonable time frame to appropriately dosed antiviral therapy. If acyclovir resistance is suspected, foscarnet is the alternative agent of choice due to low cross-resistance between the two classes of antivirals [35].

In patients who develop secondary retinal detachment during the cicatricial phase, surgical repair is successful, and there is no difference in rate of recurrent RD with pars plana vitrectomy versus combined pars plana vitrectomy with scleral buckle [37]. There is a high rate of re-detachment after initial retinal detachment repair, with 6 of 13 eyes having developed recurrent retinal detachment within the first postoperative year in one series by Kopplin et al. [37].

Some practitioners have advocated for the use of prophylactic laser retinopexy to prevent retinal detachment during the cicatricial phase. However, studies assessing outcomes are limited by selection bias, as laser retinopexy requires relatively clearer media and those patients tended to have better starting visual acuity and lesser degree of retinitis involvement [27]. The American Academy of Ophthalmology does not specifically recommend this practice due to insufficient evidence to conclude a benefit [27].

Early vitrectomy prior to retinal detachment has also been proposed as another prophylactic treatment to improve long-term visual outcomes. Potential benefits include removal of inflammatory mediators in the vitreous cavity, removal of tractional membranes, application of prophylactic laser, and placement of long-term tamponade [27]. Studies show mixed results of visual and anatomic benefit, and the American Academy of Ophthalmology found insufficient evidence to conclude whether benefit existed. Intervention prior to the lifting of the hyaloid face in patients without pre-existing PVD can be considered, as hyaloidal traction is a likely inciting factor of retinal detachment in many of these cases.

Commonly, HSV and VZV retinitis will appear to worsen slightly following the initiation of therapy; this is likely due to greater involvement of the retina than is visualized on initial exam. In a natural history study of ARN, progression of retinal lesions was occasionally observed within the first 48 hours, and regression was observed a mean 3.9 days after initiation of antiviral therapy. It is also common to see an inflammatory response, such as progression of vitritis, following initiation of therapy, which has been speculated to reflect immunologic mechanisms rather than infectious progression [38]. With treatment, the areas of retinal whitening will pigment at the edges first, following a centripetal pattern.

The anticipated visual prognosis of HSV/VZV retinitis is dependent upon the degree and location of retinitis noted at presentation, as well as other associated ocular findings. There is a correlation between the extent of retinal involvement and worse visual outcome [39], and retinitis

involving the macula was a common etiology of visual acuity worse than 20/40 [38]. Retinal arterial sheathing, sclerosis, and dye leakage on fluorescein angiography in a diffuse pattern extending from the optic nerve (rather than limited to areas of peripheral retinal involvement) are associated with poor visual prognosis [40], as they can lead to secondary ischemic optic neuropathy or large areas of retinal hypoxia. Optic nerve dysfunction, which can clinically present as an edematous or pale optic disc, can be ischemic or infiltrative (by immune cells) [38, 41]. It is also associated with worse visual acuity outcomes and is common in eyes with greater than 50% retinal involvement [38, 39]. Finally, retinal detachment is a significant cause of vision loss following ARN [38, 39].

CMV Retinitis

CMV retinitis has historically required inpatient admission for induction therapy with intravenous ganciclovir 5 mg/kg twice daily, with subsequent transition to oral maintenance therapy. First-line induction therapy is oral valganciclovir 900 mg twice daily for 3 weeks. Multiple recent studies have demonstrated that valganciclovir achieves comparable plasma drug levels and area under curve compared to intravenous ganciclovir [42]. There was no difference in relative risk of retinitis progression with valganciclovir compared to intravenous ganciclovir induction [42]. Additionally, valganciclovir is cost-effective compared to traditional intravenous induction regimens due to costs associated with inpatient admission and management of complications associated with intravenous drug administration or prolonged hospital stay [43].

Antiviral resistance is more common in CMV than in HSV or VZV and can occur through multiple known mutations including UL54 mutations which instill resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir. Letermovir resistance can occur with UL56, UL51, or UL89 mutations. Maribavir resistance can develop through UL97 kinase mutations [44]. Resistance and disease progression are associated with plasma CMV viral load above 400 international units in spite of therapy, persistent retinitis in spite of the use of a ganciclovir implant, breakthrough infections that occur on chemoprophylaxis, or failure of infection to respond clinically in a reasonable time frame [13]. Of note, immune reconstitution inflammatory syndrome (IRIS) following initiation of antiretroviral therapy in HIV patients with CMV retinitis can mimic worsening of retinitis without true antiviral resistance [14, 45]. The incidence of immune recovery uveitis is estimated to be around 0.1 per person-year and is typically associated with cystoid macular edema, epiretinal membrane formation, and neovascularization of the disc [46]. Patients with larger areas of CMV retinitis involvement are at greater risk for the development of immune recovery uveitis [47].

Adverse effects of valganciclovir include the risk of myelosuppression and nephrotoxicity, which can limit its use in some patients.

The intravitreal ganciclovir implant (Vitrasert, B&L) was previously used for the treatment of CMV retinitis during the era of HIV/AIDS prior to the advent of modern-day antiretroviral therapy. The implant is placed surgically and releases 1mcg/hr over a period of 5 to 8 months [48]. It was shown to slow time to progression in the affected eye [49]; however, local therapy with the implant alone was associated with contralateral eye involvement and systemic disease [13, 50]. Systemic therapy is superior to intraocular therapy in reducing mortality, incidence of visceral CMV disease, and contralateral eye involvement [13, 50]. Despite the relative superiority of systemic therapy in reducing contralateral eye involvement in HIV patients, the risk remains 26.1% per person-year, which is still considerable [51]. Reported ocular complications associated with the ganciclovir implant include cataract formation, vitreous hemorrhage, retinal detachment, endophthalmitis, and epiretinal membrane formation [52, 53]. The implant was discontinued in 2013 due to declining incidence of CMV retinitis in the setting of improved systemic therapeutics for HIV/AIDS.

Intravitreal foscarnet (2.4 mg/0.1 mL) is a useful intravitreal agent at the time of clinical diagnosis while awaiting molecular confirmation, due to

its efficacy against VZV, HSV-1,2, and CMV. Intravitreal ganciclovir (2 mg/0.1 mL) and cidofovir (20 mg/0.1 mL), in contrast, are solely effective against CMV retinitis, but may be administered in patients with CMV-positive aqueous PCR as monotherapy or adjunctive therapy, specifically with contraindications to or dose restrictions of systemic therapy or sight-threatening lesions. Due to lack of widespread availability of intravitreal foscarnet, intravitreal ganciclovir is sometimes used for non-CMV retinitis, but should be used only in conjunction with systemic valacyclovir therapy for adequate coverage. Due to the relatively short half-life, twice weekly injections are recommended initially and can be spaced out as retinal lesions begin to pigment.

Other FDA-approved therapies for CMV retinitis include intravenous foscarnet or cidofovir, both of which are associated with nephrotoxicity that can limit systemic administration in patients with underlying renal dysfunction [54]. Fomivirsen (intravitreal) is also FDA-approved as a second-therapy; because it is only available intravitreally, there is minimal systemic absorption and minimal systemic side effects [54]. However, as with the ganciclovir implant, it was withdrawn from market due to decreased demand for intravitreal CMV therapy with improved control of HIV/AIDS.

For patients with HIV infection, initiation of highly active antiretroviral therapy (HAART) is indicated to address the underlying immunocompromise.

The expected course of CMV retinitis can be similar to that of HSV and VZV retinitis, with slight worsening prior to improvement. Visual prognosis of CMV retinitis is often better than that of HSV and VZV, primarily due to the fact that CMV retinitis is more commonly localized to one quadrant and progresses at a slower rate [55]. However, in cases with optic nerve involvement or extensive retinitis at presentation, prognosis can be poor. Similar to HSV and VZV retinitis, retinal lesions in CMV responding to therapy should pigment at the edges and move centrally. Many practitioners advise patients to remain on lifelong antiviral prophylaxis in the absence of any contraindications. In cases of CMV retinitis, if the underlying risk factor was reversible immunocompromise such as untreated HIV infection/AIDS, antiviral prophylaxis can be discontinued after reconstitution of sufficient T-cell count with HAART [56, 57].

Cases

Case 1: VZV Acute Retinal Necrosis

A 77-year-old Caucasian woman presented for 3-week history of blurred vision in the left eye. She had been initially treated with tobramycin eye drops for redness and irritation without benefit. Her medical history was significant for rheumatoid arthritis, for which she was being treated with prednisone 10 mg daily and methotrexate 12.5 mg weekly, and two prior shingles episodes involving the right forehead and back of the neck. The rest of her medical history was noncontributory. On exam, her BCVA was 20/25 and 20/40, and IOP was 8 and 10 in the right and left eyes, respectively. Anterior slit lamp examination revealed a quiet anterior chamber and vitreous cavity and early cataracts. Dilated fundoscopic exam revealed confluent peripheral retinal whitening in the left eye, with multifocal patches of retinal whitening and few intraretinal hemorrhages extending posteriorly without macular or optic disc involvement and extensive retinal arteriolar sclerosis (Fig. 5.1). Optical coherence tomography (OCT) demonstrated pre-retinal opacities and outer retinal changes (Fig. 5.2). An anterior chamber paracentesis was performed, and aqueous fluid was sent for VZV, HSV, CMV, and Toxoplasma PCR. Intravitreal foscarnet 2.4 mg/0.1 ml was administered, and the patient was started on valganciclovir 2 mg three times daily. The aqueous sample tested positive for VZV by PCR. The patient was re-examined 2 days later with slight progression of retinitis. However, the retinitis stabilized and then began to pigment at the borders with continued foscarnet injections. The patient received biweekly

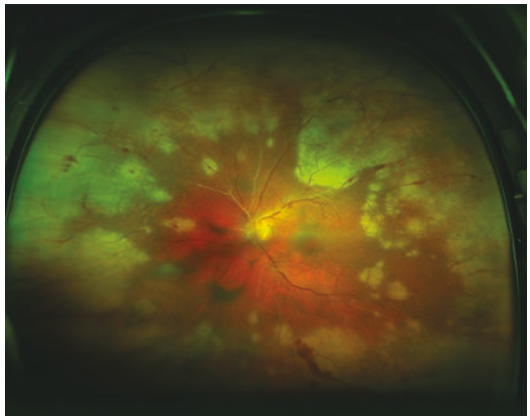

Fig. 5.1 Wide-field fundus photo of active phase of acute retinal necrosis

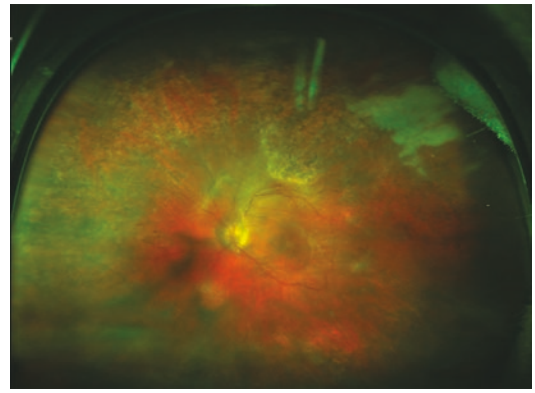

Fig. 5.3 Resolved acute retinal necrosis with proliferative vitreoretinopathy (cicatricial phase)

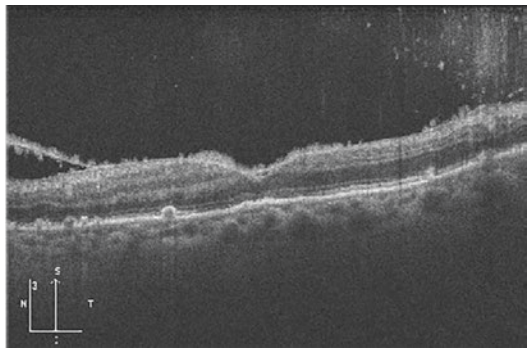

Fig. 5.2 OCT of acute retinal necrosis

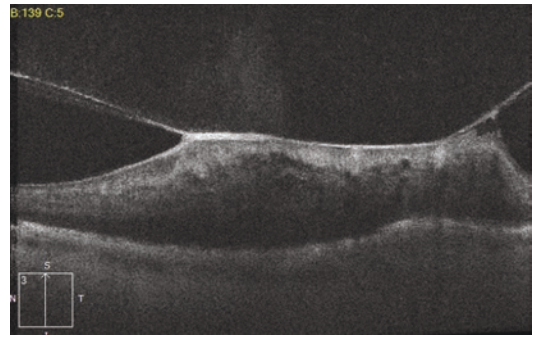

Fig. 5.4 OCT of proliferative vitreoretinopathy (cicatricial phase)

intravitreal foscarnet for total of four doses, after which it was reduced to once weekly once pigmentation was observed at multiple lesion borders. Injections were stopped once all borders of retinitis appeared fully pigmented. The patient was also initially started on topical prednisolone eyedrops and oral prednisone 20 mg daily for an expected increase in anterior chamber and vitreous cell around 2 weeks after initial presentation. Steroid therapy in conjunction with local and systemic antiviral therapy led to clinical improvement. Three months later, exam and imaging showed resolution of active retinitis with residual peripheral retinal atrophy and proliferative vitreoretinopathy without retinal detachment (Figs. 5.3 and 5.4).

Case 2: CMV Retinitis

A 58-year-old African man presented with right eye pain and vision loss. His medical history included Type 1 diabetes mellitus and pulmonary sarcoidosis. One week prior to referral, he had been diagnosed with iritis by an outside practitioner and started on prednisolone and cyclopentolate. Right eye visual acuity was 20/125, decreased from 1 week prior. Slit lamp exam revealed extensive keratic precipitates and both anterior chamber and vitreous cells in the right eye. Fundoscopic exam demonstrated vascular sheathing and multiple areas of retinitis bilaterally, right eye worse than left (Fig. 5.5a, b). His

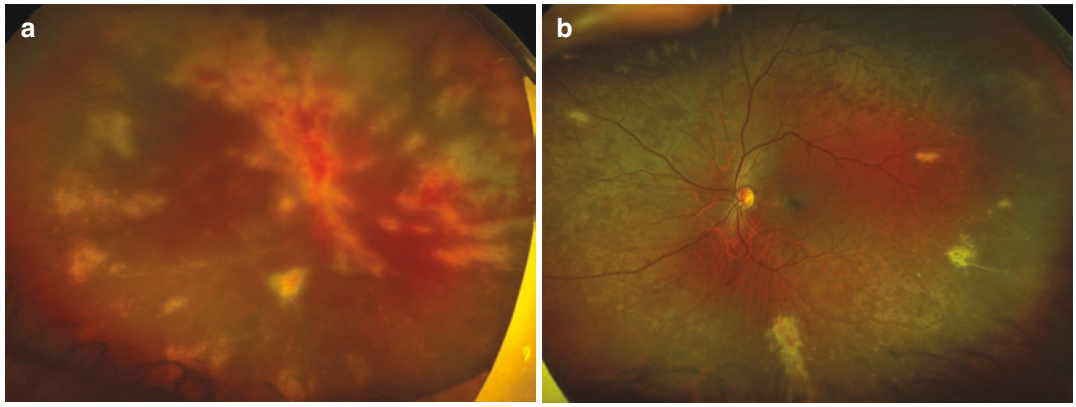

Fig. 5.5 (**a**, **b**) Bilateral CMV retinitis, with asymmetric involvement of right eye

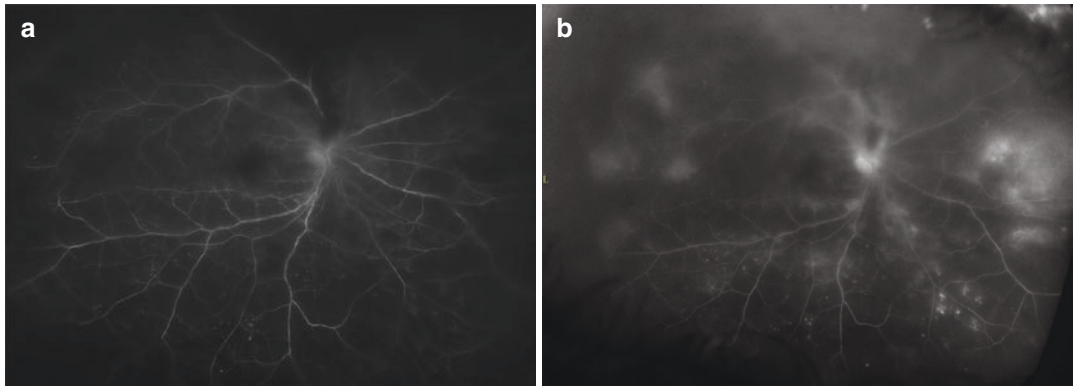

Fig. 5.6 (**a**, **b**) Fluorescein angiography of CMV retinitis, right eye. (**a**) Early frames demonstrate areas of nonperfusion and leakage against background of diabetic retinopathy. (**b**) Late frames show progressive leakage from areas of retinitis and nerve, some blockage by areas of intraretinal hemorrhage

exam also demonstrated right optic disc elevation. Fluorescein angiography demonstrated retinal vascular leakage (Fig. 5.6a, b). An anterior chamber tap was performed, and the patient received intravitreal foscarnet 2.4 mg/0.1 mL in both eyes. He was empirically started on valacyclovir 2 g three times a day, and prednisolone was increased to hourly. The aqueous sample was submitted for PCR for CMV, HSV, VZV, and toxoplasma, in addition to serological testing for HIV, syphilis, and tuberculosis, and to assess baseline hematological, renal, and hepatic status. His aqueous sample PCR was positive for the presence of CMV, and his lab results led to a new diagnosis of HIV infection. He was referred to infectious diseases and started on highly active antiretroviral therapy (elvitegravir, cobicistat, emtricitabine, and tenofovir). He was switched from valacyclovir to valganciclovir 900 mg twice daily, with plans for monitoring via weekly complete blood count. He was treated with twice weekly intravitreal foscarnet injection initially and then decreased to once weekly injections until resolution of active retinitis. As his retinitis improved, prednisolone was weaned to once daily, and valganciclovir was decreased to 900 mg daily.

Six months after initial presentation, he was noted to have bilateral recurrence of CMV retinitis. At that time the infectious diseases specialist recommended a course of intravenous ganciclovir 5 mg/kg twice daily via a peripherally inserted central catheter (PICC line). A repeat aqueous paracentesis was performed which confirmed

persistence of CMV intraocularly. He received adjunctive intravitreal foscarnet in addition to IV ganciclovir. The active retinitis resolved in the right eye and improved substantially in the left eye, and he was transitioned back to oral valganciclovir 900 mg twice daily after 6 weeks. Due to his protracted course, there was suspicion of ganciclovir resistance, but insufficient quantity of aqueous humor could be obtained for susceptibility testing. A small amount of active retinitis persisted in the left eye.

Around 9 months after initial presentation, the patient developed a new right rhegmatogenous retinal detachment with subretinal fluid encroaching into inferior macula beyond the arcades. He underwent repair with combined pars plana vitrectomy with silicone oil and scleral buckle of the right eye.

Conflicts of Interest The authors attest they have no relevant conflicts of interest to the material discussed.

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