Viral Retinitis

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Necrotizing Herpetic Retinitis

Necrotizing herpetic retinitis defines a spectrum of disease secondary to herpes viruses, specifically herpes simplex virus 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), and cytomegalovirus (CMV).

Acute Retinal Necrosis

Background

Acute retinal necrosis (ARN) is an ocular inflammatory syndrome typically seen in immunocompetent patients. Urayama first reported a constellation of findings including acute necrotizing retinitis, retinal arteritis, and subsequent retinal detachment [65]. The association of herpes viruses with ARN was first confirmed with the isolation of VZV, HSV-1, and HSV-2 from tissue cultures of vitreous and aqueous specimens and immunocytology [13, 14, 55]. Although ARN is a clinical syndrome, polymerase chain reaction (PCR) of the vitreous and aqueous specimens is sensitive and specific for confirming the causative viral agent.

Clinical Features and Diagnostic Criteria

Patients typically present with findings of ocular pain, photophobia, redness, blurred vision, and floaters [59]. The 1994 American Uveitis Society guidelines specify the

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following five clinical features for the diagnosis of ARN: (1) focal well-demarcated area of retinal necrosis in peripheral retina, (2) rapid progression of disease without antiviral therapy, (3) circumferential progression of necrosis, (4) occlusive vasculopathy, and (5) prominent inflammatory reaction in vitreous and anterior chamber [28]. There is a slight predilection to males, and it typically affects patients aged 20–60 [15, 16]. Anterior segment findings include conjunctival injection, fine or granulomatous keratic precipitates, and anterior chamber and vitreous cells. Posterior segment findings include vitreous cell and haze, areas of retinal whitening/necrosis, arteriole narrowing and sheathing of large retinal vessels, and scattered hemorrhages [15, 16]. The disease tends to progress rapidly within days to weeks from the periphery to the macula. The affected areas become thin and atrophic, frequently complicated by full thickness retinal holes. Expectedly, rates of retinal detachment are as high as 80% in some studies and are both rhegmatogenous and tractional in nature [41].

Progressive Outer Retinal Necrosis

Progressive outer retinal necrosis (PORN) is characterized by deep, multifocal, white/yellow retinal lesions which progress rapidly [18, 20]. The condition is exclusively seen in immunocompromised patients, particularly those with HIV/AIDS and CD4 counts less than 50 cells/uL. VZV antigen has been isolated from chorioretinal and vitreous specimens of patients affected with PORN [46]. The etiology is similar to ARN, involving reactivation of a latent herpes infection, but there are distinguishing clinical features.

Clinical Features

Patients initially present with painless disturbance in peripheral vision. On examination, intraocular inflammation is typically absent. Fundus exam shows areas of multifocal retinal necrosis with opacification in the outer retina [20]. Without therapy, the necrosis rapidly progresses to involve the entire retina in a circumferential fashion. Resolution during this process may present with perivenous clearing within areas of retinal whitening with a “cracked mud appearance” [18]. Retinal detachments frequently occur secondary to thin necrotic retina.

PORN Versus ARN

ARN and PORN represent a spectrum of herpetic retinitis (Table 1). ARN is associated with an exuberant inflammatory response, whereas in PORN, there is little intraocular inflammation. In PORN, macular involvement tends to be earlier, with rapid progression starting centrally and spreading in a nonspecific pattern in direct contrast to ARN’s circumferential spread from the periphery. Furthermore, PORN

Table 1 Clinical features of necrotizing herpetic retinitis

	ARN	PORN	CMVR
Symptoms	Eye pain Redness Decreased peripheral vision Floaters Photophobia	Painless Decreased peripheral vision	Painless Decreased peripheral or central vision May be asymptomatic
Clinical features	Peripheral retinal whitening Vasculitis Vitritis	Multifocal deep retinal white lesions that become confluent Early posterior pole involvement	Perivascular retinitis Hemorrhages Granular borders
Immune status	Immunocompetent	Immunocompromised	Immunocompromised
Focus	Multifocal	Multifocal	Single focus
Vasculitis	Yes	No	Variable
Vitritis	Common	Uncommon	Less common
Progression	Rapid	Rapid	Slow
Pattern of progression	Circumferential from periphery	Central and nonspecific	Perivascular
Management	Systemic antiviral Intravitreal antiviral Prednisone	Systemic antiviral Intravitreal antiviral HAART	Systemic antiviral Intravitreal antiviral HAART

tends to be a multifocal disease without granular borders, whereas ARN tends to have discrete borders [18].

Differential Diagnoses

The differential for necrotizing herpetic retinitis should include any diseases that cause retinal whitening. Infectious possibilities include CMV retinitis, toxoplasma chorioretinitis, and ocular syphilis. Autoimmune diseases include Behcet's disease, acute multifocal hemorrhagic retinal vasculitis, and sarcoidosis. Neoplastic and vascular etiologies include intraocular lymphoma, retinal artery occlusion, and retinoblastoma [16].

Imaging

Fluorescein Angiography/Indocyanine Green Angiography

Fluorescein (FA) and indocyanine green (ICG) angiography is not necessary for diagnosis of acute retinal necrosis, and has limited utility in cases with severe vitritis, but can be helpful in delineating the extent of disease (Table 2). During active disease, capillary non-perfusion is noted in affected areas as well as leakage of the few perfused

Table 2 Imaging features in viral retinitis

	FA	ICG	OCT	FAF
ARN: active disease	Capillary non-perfusion and leakage of major vessels Vascular occlusion Abrupt demarcation in perfusion Late optic disc staining	Limited leakage of retinal vessels	Inner retina hyperreflectivity Macula edema/ exudates Retinal traction	Hyperfluorescent border
ARN: treated	Window defects		Retinal thinning/ atrophy Loss of ellipsoid in macula disease	
PORN: active disease	Early blockage/ late staining Retinal leakage in areas of retinal whitening		Outer retinal thickening and hyporeflectivity	Hypoautofluorescence
PORN: treated	Widespread late leakage of choriocapillaris		Retinal thinning/ atrophy RPE irregularity	Stippled hyperfluorescence with retinal atrophy
CMVR: active disease	Microaneurysms Blocking in areas of hemorrhage Leaking or non-perfusion of vessels in affected areas	Hypocyanescence in areas of retinal edema/ inflammation	Full thickness retinal edema Foveal and parafoveal inner retina reflectivity	Hyperautofluorescence of active borders Hypofluorescence in areas of full thickness retinitis
CMVR: treated	Staining due to window defects	Staining due to window defects	Retinal thinning, choroid hyperreflectivity Cystoid macula edema from immune-recovery uveitis Epiretinal membrane/ vitreoretinal traction	Mottled hyper and hypoautofluorescence in healing

major vessels [71]. Obstruction of the central retinal artery or one of its branches has been reported [16]. Areas of acute retinitis show an abrupt demarcation in perfusion of both arteries and veins (Fig. 1) [16]. Other findings include late staining of the optic disc during the recirculation phase and perifoveal leakage [16]. After disease resolution, window defects may be seen in previously affected areas due to RPE abnormalities [16]. ICG leakage from retinal vessels was much more limited [63].

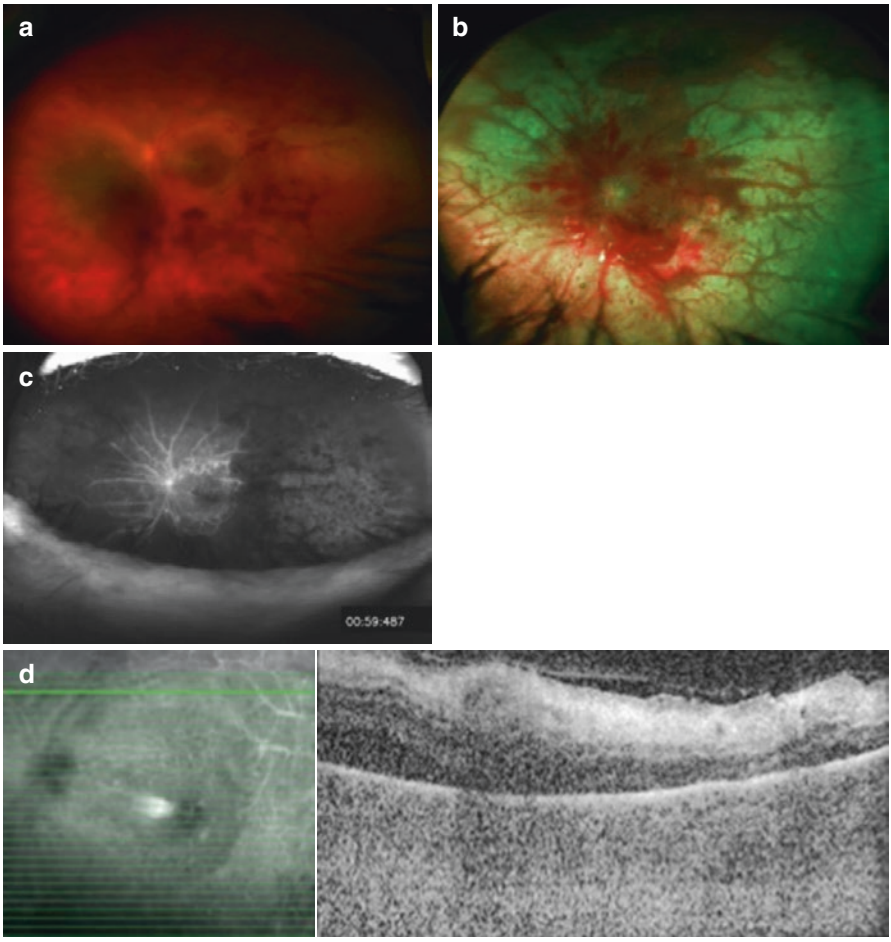

Fig. 1 Acute retinal necrosis. (**a**) Acute retinal necrosis with significant vitritis, peripheral areas of hemorrhage, and retinitis. (**b**) Follow up image after pars plana vitrectomy with 360 degrees of retinitis and hemorrhage. (**c**) Fluorescein angiogram showing extensive retinal ischemia and blockage from hemorrhages. (**d**) SD-OCT with inner retinal hyperreflectivity. (Figures courtesy of Dr. William Mieler)

In progressive outer retinal necrosis, FA has provided insights into disease evolution. Early in the course of disease, the multifocal peripheral lesions display early blockage and late staining [20, 46]. Beyond these areas of punctate retinal whitening, however, extensive retinal microvascular alterations (capillary loss and microaneurysms) of the equatorial and peripheral retina have also been noted [67]. Larger more confluent areas of retinal whitening displayed retinal leakage. Despite treatment with parenteral antivirals, the disease can progress with extensive damage to the RPE manifesting as widespread late leakage of the choriocapillaris on fluorescein angiography. As the disease reactivates, a "brush-fire" pattern of leakage from the choriocapillaris at the border of normal and affected retina appears [67].

Optical Coherence Tomography

Optical coherence tomography (OCT) is an imaging technique that provides visualization of optical cross-sectional images of the ocular tissues using low coherence interferometry [32]. Suzuki et al. described time domain OCT findings in seven eyes in seven patients with ARN [62]. Acutely, in areas of retinal whitening, OCT showed highly reflective inner retina lesions and obscuration of the retinal architecture. This has also been noted in spectral domain (SD) and swept source (SS) OCT [51]. Macular edema and exudates have also been noted in the acute phase [50]. SD-OCT has also been used outside of the macula to image areas of peripheral retinitis with findings of full thickness retinal hyperreflectivity and intraretinal and subretinal cysts [40]. With initiation of antiviral treatment and normalization of the retina appearance clinically, OCT shows marked retinal thinning and atrophy [50, 51, 62]. In patients with macular disease at presentation, the ellipsoid layer did not recover despite disease regression and visual acuity remained poor [51]. With worsening of intraocular inflammation, SD-OCT findings of inflammatory retinal traction and eventual development of combination tractional/rhegmatogenous detachment have been reported [40].

Time domain OCT of HIV-positive patients with VZV-related PORN show acute findings of outer retina thickening and hyporeflectivity [3, 7, 11]. After treatment, the areas which appear atrophic on clinical exam demonstrate thinning, loss of identifiable retinal structures, and RPE irregularity on OCT (Fig. 2) [3, 11]. Several months after treatment, OCT demonstrated full thickness neurosensory atrophy of the central macula [7]. The authors feel that the disease presents as an outer retinal disease but will eventually involve the full thickness of the retina [7]. This notion

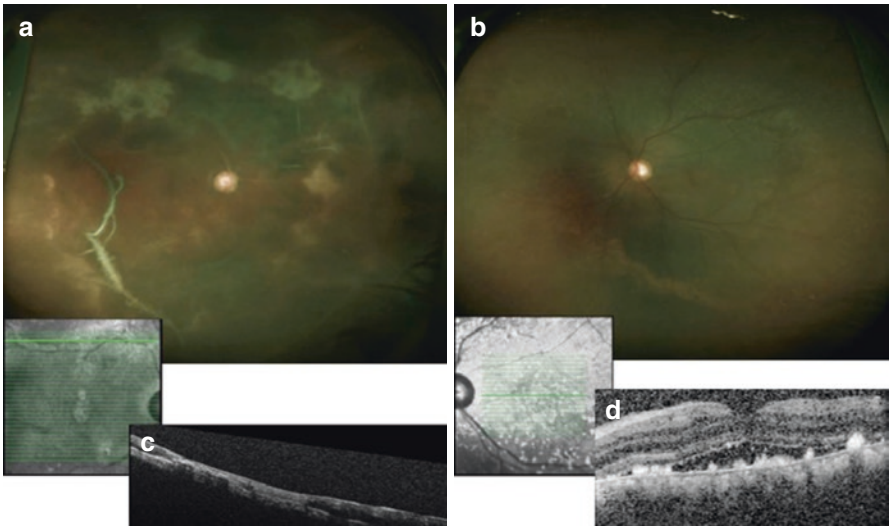

Fig. 2 Progressive outer retinal necrosis. (**a**) Right eye and. (**b**) Left eye showing multifocal, deep retinal lesions in the periphery and perivascular whitening. (**c**) SD-OCT macula of right eye with retinal hyperreflectivity and thinning in areas of retinitis. (**d**) SD-OCT macula of left eye with subretinal deposits, full thickness retinal hyperreflectivity. (Figures courtesy of Dr. Felix Chau)

has recently been debated as histological studies of early PORN show relative sparing of the outer retina [45]. Others have proposed that PORN begins with deep capillary ischemia [72]. Further imaging studies with high-resolution OCT and OCT angiography may provide more insights into the disease process.

Fundus Autofluorescence

Fundus autofluorescence (FAF) imaging allows for a topographic map of lipofuscin accumulation in the RPE, and autofluorescence is thought to precede frank photoreceptor degeneration. Patients with PORN acutely show areas of hypofluorescence due to obscuration by retinal opacification which later become stippled with hyperfluorescence as these opacified areas atrophy on funduscopy [11]. FAF changes in progressive outer retinal necrosis are delayed compared to clinical findings and appear subsequent to lipofuscin accumulation in areas of retinal inflammation. FAF offers higher contrast delineation of ARN lesions with a hyperfluorescent border which may assist in monitoring of disease progression [68].

Treatment

Systemic antiviral therapy was first shown to be effective for the treatment of herpetic retinitis in the 1980s with intravenous acyclovir [8, 27]. Since then, newer antiviral agents such as valacyclovir (acyclovir prodrug) and famciclovir (prodrug of penciclovir) which can achieve systemic levels similar to that of intravenous acyclovir obviated the need for patients to be hospitalized [1, 5, 17]. Additionally, oral antivirals were shown to be beneficial for preventing fellow eye involvement [52].

Adjunctive Therapy with Intravitreal Antiviral Injections

The addition of intravitreal antiviral agents was first shown to be effective in HIV-positive patients with PORN [57]. Subsequently, successful results with adjunctive therapy with intravitreal antivirals in patients with ARN were described in several series [38, 44, 64]. Combination systemic and intravitreal antiviral therapy is now considered the standard of care for necrotizing herpetic retinitis. Patients receiving combination systemic and intravitreal antiviral therapy are more likely to have improvement in visual acuity and lower incidence of retinal detachment than those treated with systemic therapy alone [19].

Laser

Prophylactic laser to uninvolved retina adjacent to diseased retina can decrease the rates of progression to retinal detachment, although this remains controversial [25, 61]. More severe cases tend to be treated with laser but also have higher rates of retinal detachment [53].

Role of Surgery

Retinal breaks and rhegmatogenous retinal detachment are a frequent complication of herpetic retinitis, in up to 50–80% of cases [12, 24, 41]. Although retinal detachment repair with pars plana vitrectomy, scleral buckle, long-acting gas, or silicone oil tamponade has been successful, many patients require more than one surgery, and visual acuity may remain poor after surgery despite successful reattachment [2, 12, 48, 60]. Early or prophylactic vitrectomy by removing inflammation and preventing detachment has been explored but remains controversial [6, 33, 43].

CMV Retinitis

Cytomegalovirus (CMV) retinitis is seen exclusively in immunocompromised patients, particularly in HIV/AIDS, or as a result of congenital infection. Risk factors for CMV retinitis include CD4 T cell counts <50 cells/uL and presence of one or more opportunistic infections [39]. However, CMV retinitis may also occur after solid organ or allogeneic bone marrow transplantation especially in the case of CMV-negative patients and CMV-positive donors [34].

Clinical Findings

Unlike necrotizing retinopathies caused by HSV and VZV, CMV retinitis is a more slowly progressive disease [29–31]. Patients may be asymptomatic or present with decreased visual acuity. Vitritis is usually absent. There are variations in presentation of CMV retinitis, including (1) hemorrhagic retinitis within the posterior pole distributed along retinal vasculature; (2) a granular, indolent form with active retinitis at borders of the lesion; and (3) a perivascular or frosted branch angiitis [10, 21].

Imaging

Ultrawide-field fundus imaging (UWF) which captures approximately 200° of the retina has been used to monitor disease progression in CMV retinitis (Fig. 3). In one study comparing UWF imaging with the Optos system to standard montage fundus photography, UWF imaging captured 40% more CMV affected areas compared to standard photography [49]. UWF provides improved monitoring of peripheral lesions and response to treatment.

Fluorescein angiography highlights vascular abnormalities such as enlarged foveal avascular zone, microaneurysms, hypofluorescence in areas of retinal edema and inflammation, as well as marked vascular leakage [22].

SD-OCT findings in three patients with active CMV retinitis showed full thickness retinal edema and disruption of retinal architecture in affected areas of retina (Fig. 4) [40]. As the lesions healed with treatment with antivirals, retina thinning

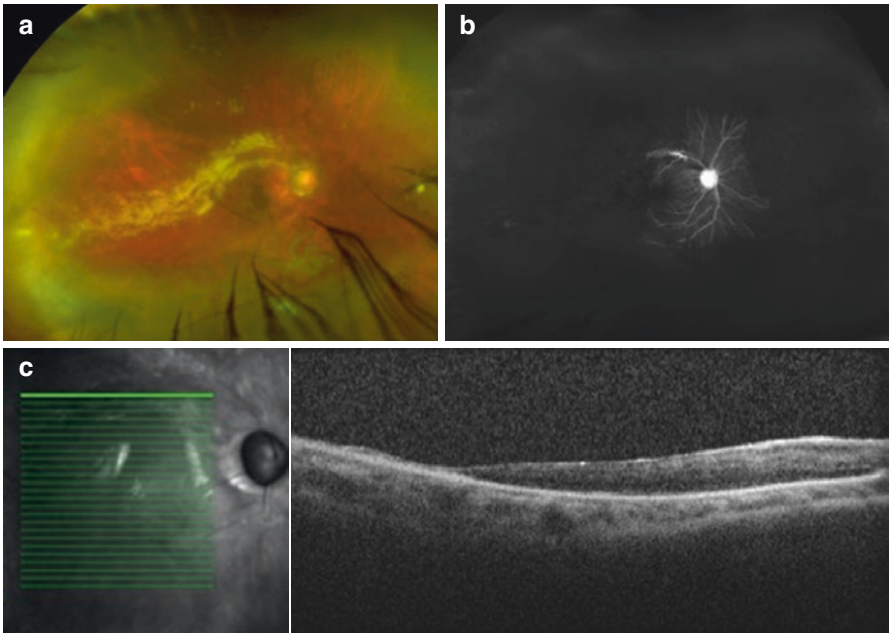

Fig. 3 CMV retinitis. (**a**) Ultrawide-field image demonstrating perivascular distribution of fluffy white retinal infiltration and small areas of hemorrhage along superior arcade. (**b**) Fluorescein angiogram demonstrating extensive retinal ischemia. (**c**) SD-OCT macula showing loss of retinal tissue in areas of retinal whitening. (Figures courtesy of Dr. Lawrence Ulanski)

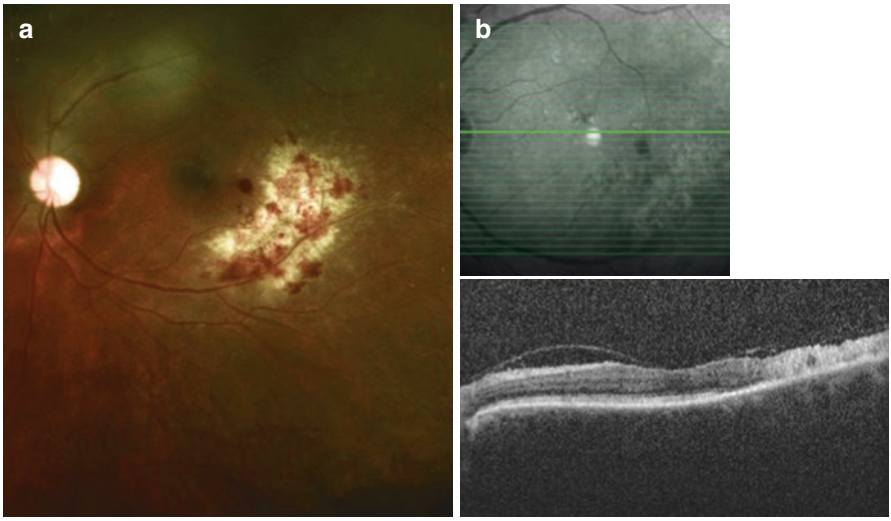

Fig. 4 CMV retinitis. (**a**) Focal area of hemorrhage and perivascular infiltrate. (**b**) SD-OCT showing disruption of retinal architecture and full thickness retinal hyperreflectivity in affected area. (Figures courtesy of Dr. Felix Chau)

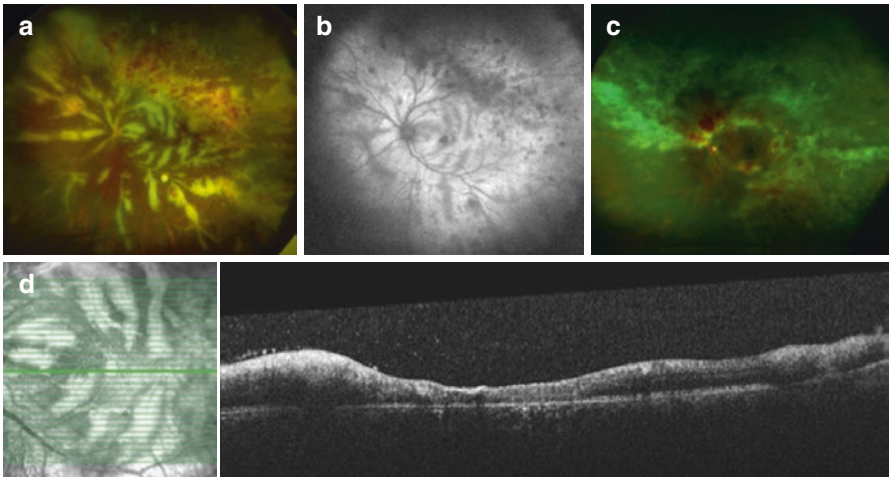

Fig. 5 CMV retinitis. (**a**) Frosted branch angiitis with extensive perivascular infiltrates and hemorrhage. (**b**) Autofluorescence image with hypoautofluorescence in areas of perivascular infiltrates. (**c**) Resolving perivascular infiltrates and hemorrhages. (**d**) SD-OCT showing inner retina hyperreflectivity and retinal edema in area of active retinitis and atrophy, loss of retinal architecture in inactive or resolving areas. (Figures courtesy of Dr. Yannek Leiderman)

and choroid hyperreflectivity secondary to RPE atrophy were apparent on OCT [40]. An additional finding is that of cystoid macular edema, thought to be secondary to immune-recovery uveitis. SD-OCT can help distinguish retinitis from a cotton wool spot which can also be seen in patients with HIV and only affects the inner retina [40]. Inner retinal hyperreflectivity, corresponding to areas of retinal ischemia on FA, has also been seen. With treatment, there is reduction in retinal thickness [4].

SD-OCT has also been used to study the vitreoretinal interface. In 42 eyes from 21 patients with healed CMV retinitis scars, a majority had abnormalities including epiretinal membrane and vitreoretinal gliosis, which may provide further explanation for high rates of retinal detachment in patients with CMV retinitis [9].

FAF imaging in active CMV retinitis demonstrates hyperautofluorescence at the active borders of affected areas, while areas of full thickness retinitis in the posterior pole were hypoautofluorescent (Fig. 5) [70]. Mottled regions of hyper- and hypoautofluorescence corresponded to either RPE atrophy or various stages of healing. In this series, FAF was particularly helpful for patients with subtle findings of disease activity on clinical exam by highlighting disease recurrence with hyperautofluorescence at the active borders in patients previously affected by CMV on chronic antiviral therapy [70]. With treatment of CMV retinitis, the hyperautofluorescent borders seemed to decrease.

Treatment

The use of highly active antiretroviral therapy (HAART) significantly reduced the incidence and severity of a number of opportunistic infections in HIV/AIDS

patients, including CMV retinitis. Anti-CMV therapy, however, still plays a critical role for treatment of CMV retinitis in the HAART era. Intravenous antiviral treatment options include ganciclovir, foscarnet, and cidofovir. Oral antivirals include valganciclovir, a prodrug of ganciclovir. Intraocular agents include intravitreal ganciclovir and foscarnet and a long-acting ganciclovir implant. Systemic antiviral therapy prevents dissemination of the virus either to the second eye or elsewhere in the body. Anti-CMV therapy improved mortality for HIV-infected patients, even with the widespread use of HAART therapy [35]. Combination systemic and intravitreal therapy, as well as treatment of HIV with HAART, is considered to be the standard approach for treatment of HIV-positive CMV retinitis patients [35].

Epstein-Barr Virus and Ebola Virus

Epstein-Barr virus (EBV) has been implicated in cases of bilateral uveitis, keratitis, conjunctivitis, and ARN following viral reactivation [47, 69]. However, EBV is present ubiquitously in mucosal tissue, and the pathogenesis of EBV in viral retinitis is unclear. Most cases that have isolated EBV in diseased eyes reported coinfection with VZV [26, 41], and therefore its role as a causative agent in ocular pathology is difficult to discern. Two recent case studies have reported EBV as a sole causative agent of ARN by immunohistopathologic confirmation of positive EBV titers [23, 56].

The recent outbreak of Ebola has led to reports of Ebola-related ocular disease. Although the pathogenesis of Ebola-related uveitis is unclear, anterior uveitis and panuveitis have developed during the convalescent stage in Ebola survivor patients [66]. 21 out of 96 Ebola survivors developed an Ebola virus disease-related uveitis [58]. Patients present with eye pain, photophobia, and visual loss [42] with clinical findings of keratic precipitates, vitritis, peripheral chorioretinal scars, and elevated intraocular pressure as the uveitis progresses [58]. Ebola virus has been found within the ocular fluid even after clearance of viremia [66]. Whether the uveitis is caused by active viral replication, viral persistence in the eye, or immunological reaction to the virus is unclear and needs further investigation.

Imaging

One case report of EBV-associated retinitis described the use of FA, which highlighted disc leakage and retinal vasculitis at disease onset. With 4 weeks of antiviral therapy, disc edema and phlebitis improved. By 3 months of treatment, these findings had resolved [36].

Treatment

EBV lacks a virus-specific thymidine kinase; however, acyclovir has 100 times more affinity for EBV DNA polymerase than that of the human host [37]. In a meta-analysis of 45 immunocompetent patients with manifestations of infectious

mononucleosis, acyclovir was the most commonly prescribed antiviral although the role of antivirals in what is a typically self-limited viral disease has been questioned [54]. In ocular disease, the use of systemic and topical acyclovir has been described [23, 69]. Early diagnostic vitrectomy, focal panretinal photocoagulation in areas of retinal ischemia, and intravitreal antivirals have also been used as treatment in EBV-associated ocular infection [36, 56].

The treatment of Ebola-related uveitis is largely experimental. Intraocular inflammation is treated with topical, periocular, and systemic steroids [66]. Use of favipiravir, an experimental antiviral drug, has also been employed.

Conflict of Interest Ann-Marie Lobo, Mei Zhou, and Dana Darwish declare that they have no conflict of interest.

Informed Consent No human or animal studies were carried out by the authors for this article.

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