CMV Retinitis

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Introduction

Cytomegalovirus (CMV), a double-stranded DNA virus in the herpesvirus family, is a major cause of morbidity and mortality in severely immunocompromised patients. This population includes those with acquired immune deficiency syndrome (AIDS) and those with iatrogenic immune suppression such as chemotherapy, solid organ transplant recipients, and bone marrow transplantation recipients.

CMV is a fairly ubiquitous infection with an estimated 60 % or more of the general adult population in the United States showing serologic evidence of prior CMV infection [1]. Following the primary infection, CMV then remains latent in the infected host throughout life and reactivates only to cause illness in immunocompromised hosts. CMV infection is more prevalent in populations at risk for HIV infection with more than 75 % of IV drug users and more than 90 % of homosexual men having detectable IgG antibodies to CMV [2].

Retinitis is the most common clinical manifestation of CMV infection. However, systemic CMV manifestations in immunocompromised hosts also include esophagitis, colitis, pneumonitis, and neurologic disease such as encephalitis and polyradiculopathy.

There is some data to suggest that recent progress in bone marrow transplantation including increased transplantation from HLA-matched unrelated or mismatched donors, new preconditioning regimens, more aggressive treatment of graft-versus-host disease, and prolonged survival rate after bone marrow transplantation may prolong hematopoietic stem cell recipient survival and result in a growing incidence of CMV retinitis [3]. One study suggests the cumulative incidence of CMV retinitis in transplant recipients reaches greater than 2 % [4].

While the advent of highly active antiretroviral therapy has significantly decreased the incidence of CMV retinitis in the AIDS population, it continues to be an important major sight-threatening conditions in the severely immuno suppressed.

Clinical Presentation

Patients with retinitis most often present with symptoms such as decreased visual acuity, floaters, photopsia, eye pain, and scotomas.

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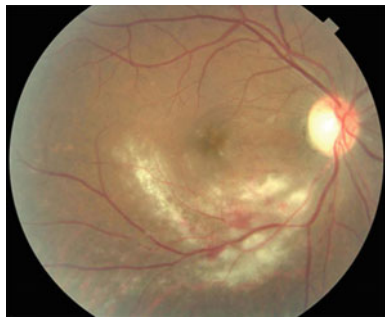

Fig. 5.1 Classic appearing CMV retinitis with white retinal lesions and hemorrhages along the arcades of the posterior pole

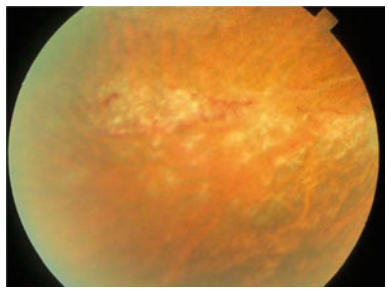

Fig. 5.2 Granular peripheral lesions that are typically seen in the peripheral retina

Photopsia and floaters are both independently significant predictors of CMV retinitis in patients with AIDS [5].

The external appearance of an eye with active CMV infection is usually white and quiet. Slit lamp exam may reveal mild inflammation including fine, stellate keratic precipitates, anterior chamber cells and a mild vitritis may be present on posterior examination.

CMV infection causes a full-thickness necrotizing retinitis that may affect the posterior pole, periphery, or both, and it can be either unilateral or bilateral. The appearance of the retinitis may be variable though the most characteristic ophthalmologic appearance consists of perivascular fluffy whitish yellow retinal lesions with intraretinal hemorrhages [6]. Early on, retinal lesions may be small, white infiltrates resembling large cotton wool spots (Fig. 5.1). These may evolve into larger creamy white geographic lesions. Retinal hemorrhages are often present along the leading edge of or within a necrotic area. Peripheral lesions may appear more granular and may not be associated with retinal hemorrhages (Fig. 5.2). Other features that may be present on retinal examination include vascular sheathing with a so-called "frosted branch angiitis" and papillitis, which may be present in 4 % of CMV patients and spread either by primary optic nerve involvement of spread from the peripapillary retina [7, 8].

Diagnosis

The differential diagnosis for CMV retinitis includes other viral retinitides, particularly those in the herpesvirus family such as acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) as well as toxoplasmosis, candidiasis, syphilis, and Behcet's disease. These can often be distinguished from CMV retinitis by clinical history and ophthalmologic evaluation.

ARN and PORN are much more rapidly progressive and present with fulminant retinal necrosis. Unlike ARN and PORN, however, CMV retinitis is usually localized to one quadrant initially and progresses more slowly. The amount of intraocular inflammation associated with CMV retinitis is minimal to nonexistent, while there is often significant intraocular inflammation associated with ARN, toxoplasmic retinitis, Candida endophthalmitis, and Behcet's disease. In addition to being marked by intraocular inflammation, even in an immunocompromised host, toxoplasmosis is generally confined to a limited portion of the retina. Moreover, in cases of reactivation, a pigmented chorioretinal scar is often found adjacent to the area of active toxoplasmic retinitis.

However, should there be uncertainty regarding the diagnosis, a polymerase chain reaction (PCR) analysis of vitreous or aqueous samples can be performed. In making the diagnosis of CMV retinitis, PCR-based analysis of vitreous tap is highly sensitive and specific; however, it is usually reserved for patients with atypical lesions or those unresponsive to treatment. The specificity of PCR testing for the

detection of CMV in vitreous and aqueous samples has a specificity of 93 % and a sensitivity of 67 % for vitreous samples and 37 % for aqueous samples according to one study [9].

The presence of CMV serum antibodies is not diagnostically useful as this only confirms prior exposure to the infection. Additionally, urine is CMV culture positive in the majority of AIDS patients, including many without CMV retinitis, rendering the test poorly specific for CMV infections.

Treatment

There are several effective pharmaceutical agents which may be administered systemically or locally for the treatment of cytomegalovirus retinitis. The choice of initial therapy for CMV retinitis should be individualized to each patient and based on several clinical factors including antiretroviral history, underlying degree and reason for immunosuppression, location of lesion, ability to adhere to treatment, and patient preference.

Ganciclovir was the first anti-CMV drug, approved for use in 1989, and it acts via competitive inhibition of CMV DNA polymerase following phosphorylation in CMV-infected cells. To achieve high tissue concentrations of the drug in the induction phase, ganciclovir must be infused intravenously at a dose of 5 mg/kg every 12 h for at least 14 days. After induction, a 5 mg/kg daily dose of intravenous ganciclovir is given indefinitely. On discontinuation of the drug, CMV retinitis can recur as early as 10–21 days at the borders of previously healed areas. Researchers have found recurrences even during maintenance therapy in about 30 % of patients [10] and a 100 % recurrence in patients with discontinuation or delay in ganciclovir therapy. [11, 12] Oral ganciclovir can be used as maintenance therapy though it is less effective than intravenous ganciclovir. Oral ganciclovir for prophylaxis or long-term maintenance treatment of CMV retinitis has been replaced with valganciclovir, which provides greater bioavailability.

Ganciclovir is excreted by the kidneys, and those with renal insufficiency need appropriate dosage adjustments. Notable medication-induced side effects include granulocytopenia, abnormal liver function tests, neurologic dysfunction, and thrombocytopenia [13–15].

Valganciclovir is an orally administered prodrug form of ganciclovir which provides greater bioavailability. It is used for both induction and maintenance therapy of CMV retinitis and is administered in a dose of 900 mg twice daily for three weeks as induction therapy followed by 900 mg daily as maintenance therapy. Orally administered valganciclovir has been shown to be as effective as intravenously administered ganciclovir for induction treatment and is an effective maintenance therapy for CMV retinitis [15, 16]. Its pharmacologic safety profile and side effects are similar to that of intravenously administered ganciclovir given it is concerted to ganciclovir in the bloodstream.

Foscarnet is a pyrophosphate analog approved for use in 1993 with broad antiviral activity against CMV and other herpes viruses as well as HIV. It is useful against strains of ganciclovir-resistant CMV due to its different mechanism of action [15, 17]. In a large, randomized trial comparing ganciclovir to foscarnet in the treatment of CMV retinitis, no difference in the rate of progression of retinitis was demonstrated in the two groups; however, foscarnet was found to offer a slight survival benefit [18]. Induction therapy with foscarnet is 90 mg/kg given intravenously over 1 h, every 12 h, for 2–3 weeks or until retinitis stabilizes. Maintenance therapy is 90–120 mg/kg given IV over 2 h, once per day. Renal function must be closely monitored and patients must be adequately hydrated while receiving the medication as the most frequently reported adverse effect with foscarnet administration is nephrotoxicity. Other adverse effects of foscarnet include abnormalities in phosphorous and calcium handling, including symptomatic hypocalcemia which can lead to arrhythmias and seizures. Other less common side effects are nausea, genital ulcers, anemia, hypokalemia, and hypomagnesemia [19].

Cidofivir is a nucleotide analog with a longer intracellular half-life which is used intravenously and is active against a broad spectrum of herpes

viruses, including CMV. Standard dosing of cidofivir is induction with weekly 5 mg/kg intravenous infusion for 2 weeks followed by maintenance therapy with 5 mg/kg every two weeks. The main side effect of the drug is nephrotoxicity, thus it is administered in conjunction with oral probenecid to reduce renal uptake of cidofivir and IV saline hydration [20, 21]. Cidofivir can also cause anterior uveitis and hypotony, thought due to its toxic effects on the ciliary body [22]. This severe renal and ocular toxicity has limited the use of cidofivir in clinical practice.

Systemic therapy reduces the likelihood of involvement of the contralateral eye and improves survival [15, 23, 24]. However, intravitreal therapy is often used to have maximal drug affect in the retina without systemic side effects. Intravitreal injections of ganciclovir or foscarnet may be used in conjunction with oral valganciclovir. This may provide for higher immediate intraocular levels of the drug and faster control of retinitis that is macula-threatening.

The ganciclovir implant, which is no longer manufactured, was able to provide control of retinitis for 6–8 months [11, 24]. Intravitreal ganciclovir is used less frequently since the introduction of HAART as the majority of patients respond to systemic anti-CMV treatment alone.

Other options for intravitreal therapy include foscarnet and cidofivir. Foscarnet is given as a 2.4 mg injection one or two times weekly and has been shown to be a safe and effective alternative treatment in patients resistant to intravenous therapy [25]. Cidofivir is injected at a 20 Âµg dose every 5–6 weeks and has been shown to be as effective as induction therapy with only rare episodes of reactivation and progression, though the known ocular complications of hypotony and iritis limit its use [26–28].

Fomivirsen is an antisense oligonucleotide that prohibits the production of messenger RNA and thus inhibits CMV replication. This drug is solely approved for intravitreal injection for CMV retinitis that has not been controlled well with other medications [29]. The drug has several toxic side effects including anterior and posterior uveitis, transient elevation in intraocular pressure, retinal pigment epitheliopathy, and bull's eye maculopathy [30].

CMV Retinitis in the Era of HAART

Highly active antiretroviral therapy (HAART) has dramatically altered not only the incidence of CMV retinitis in patients with AIDS but it has also affected the presentation and course of CMV infection.

Highly active antiretroviral therapy consists of three or more antiretroviral drugs and is composed of one or more protease inhibitor (PIs), nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and an integrase or entry inhibitor as the third agent.

HAART has led to a reduction of morbidity and mortality in HIV-infected patients through immune reconstitution in HIV patients with increased CD4 + T cell counts and decreased HIV replication [31]. CMV retinitis was the most common cause of visual impairment and vision loss in HIV-infected patients prior to the advent of HAART in 1995. Prior to this, about 25–42 % of HIV-infected patients with AIDS developed CMV retinitis and the incidence of cytomegalovirus retinitis in patients with CD4 + T cell counts less than 50 cells/mm^3 was approximately 20 % per year [32, 33]. Widespread use of HAART has led to a decrease in the annual number of new cases of CMV by more than 50 % [34].

HAART has not only reduced the risk of CMV retinitis in patients with HIV but has also altered the course. Prior to HAART, CMV retinitis, even with appropriate anti-CMV treatment, often progressed to blindness. Bilateral disease occurs less frequently in patients on HAART and anti-CMV treatment, 26 % per person-year compared with approximately 60 % per person-year in those patients not on HAART or CMV therapy [35]. Prior to the advent of HAART, time to progression of CMV retinitis was approximately 2 months in patients treated with intravenous ganciclovir or foscarnet [36], 2–

4 months with intravenous cidofivir [37], and up to 7 months with the ganciclovir intravitreal implant [24].

The advent of HAART and its resulting aid in the recovery of immune function in HIV patients has even allowed patients to discontinue their CMV treatment, whereas prior to the HAART era long-term maintenance treatment was necessary. Discontinuation of maintenance therapy has been shown to be safe in a subset of patients. Patients should have sustained CD4 count elevation of at least 100 cells/mm^3 for at least 3–6 months before discontinuing anti-CMV treatment and should be monitored carefully for reactivation [12, 38–40].

One study showed that if retinitis has adequately resolved with antiviral treatment and immune function has recovered (two consecutive CD4 + T cell counts of ≥100 cells/mm^3 at least 6 months apart) CMV therapy may be discontinued [36]. Another study showed that with discontinuation of anti-CMV therapy after persistent CD4 + T cell count over 50 cells/mm^3, 19 of 22 patients remained healed without CMV recurrence at the end of the study and the three patients who progressed had CD4 cell counts that dropped below 50 cells/mm^3 and viral loads in the hundreds of thousands, representing HAART failure [38]. This emphasizes the importance of periodic ophthalmologic monitoring in all patients, even those with successful immune recovery on HAART, as the HAART-induced elevation in CD4 count can fall allowing the recurrence of CMV infection.

Complications Related to CMV Retinitis

Retinal Detachment in CMV Retinitis

Retinal detachment is a common cause of vision loss in patients affected by cytomegalovirus retinitis. In the pre-HAART era the incidence of retinal detachment in CMV retinitis was approximately 33 % per eye per year [41]. Greater involvement of the peripheral retina and active retinitis are two significant risk factors for the development of retinal detachment in these patients [42]. Rhegmatogenous retinal detachment is associated with active retinitis due to breaks in necrotic retina. The use of HAART has resulted in a 60 % decrease in the rate of retinal detachment in AIDS patients with CMV retinitis [23]. The standard approach for the repair of these retinal detachments is a pars plana vitrectomy removal of posterior hyaloid and intraocular tamponade with silicone oil or a long-acting gas due to the propensity for multiple breaks which may not be apparent until the time of vitrectomy [41, 43]. Studies have shown no statistically significant difference in the rate of retinal reattachment or macular reattachment in patients where scleral buckle was used versus vitrectomy and silicone oil tamponade [44]. Visual acuity may continue to be compromised by silicone oil, resulting cataract formation from the oil or optic atrophy due to the disease.

Immune Recovery Uveitis

While HAART has significantly improved prognosis in HIV-infected patients, the immune reconstitution associated with antiretroviral therapy also presents additional ocular complications, most importantly immune recovery uveitis (IRU).

IRU is a syndrome that may develop in patients with cytomegalovirus retinitis who have responded to antiretroviral therapy with immune recovery and increase in CD4 + T cells. Immune recovery uveitis was first described in 1998 in patients with cytomegalovirus who experienced immune reconstitution due to highly active antiretroviral therapy [45, 46]. The incidence rate of IRU has varied among different reports from 15 to 37.5 % [12, 47].

The primary signs and symptoms of IRU include decreased vision and floaters. Clinically, this entity is characterized by signs of inflammation including iritis, vitritis, papillitis, and macular changes.

Pathogenesis of IRU is unknown, however it is hypothesized that this is an immunologic reaction to cytomegalovirus antigens in retinal tissues caused by HAART-mediated recovery in

immune status. Another hypothesis is that the control of CMV retinitis is actually incomplete and the recovered immune system is mounting an inflammatory response to virus or viral proteins. Previous treatment with cidofivir may be a risk factor for the development of IRU [48]. Similar reactions have occurred in other organs, such as fever and lymphadenitis in patients with Mycobacterium avium complex or meningitis in patients with latent cryptococcal CNS infection after the initiation of HAART [49].

Vision loss in these patients occurs from long-term complications associated with IRU. These may include posterior subcapsular cataracts, cystoid macular edema, epiretinal membrane, proliferative vitreoretinopathy, neovascularization of the disc, vitreomacular traction, and severe postoperative inflammation [50–52].

Conclusion

Cytomegalovirus retinitis may lead to significant ocular morbidity in immunocompromised patients that are not readily diagnosed and treated. The advent of HAART has transformed one of the most common intraocular infections within the United States to an entity that may be rarely seen by an ophthalmology resident during a three-year training program. Despite these advances for AIDS patients, CMV retinitis remains a concern for HIV-infected individuals not on treatment or those who have failed anti-HIV treatment as well as those immunocompromised by other means such as chemotherapy, organ transplantation, and bone marrow transplantation. With the advancement in medical therapies prolonging survival and increasing the number of these immunocompromised hosts, physicians should continue to remain vigilant and screen these patients for CMV retinitis. Regular dilated exams are recommended for these immunocompromised hosts, particularly those with CD4 + T cell counts less than 50 cells/mm^3, as these patients may remain asymptomatic due to the lack of intraocular inflammation unless a lesion involves the macula or the optic nerve. Early detection not only reduces visual loss by reducing the risk of retinal detachment and other associated ocular complications, but also decreases overall morbidity and mortality in these patients.

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