Ocular Manifestations of the Acquired Immunodeficiency Syndrome

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Ophthalmologic findings in individuals with the acquired immunodeficiency syndrome (AIDS) are fairly common. A noninfectious microvasculopathy of the retina is the most frequent manifestation. Cytomegalovirus (CMV) retinitis is the opportunistic infection most likely to cause visual loss and must be differentiated from toxoplasmosis or herpetic retinitis. Ganciclovir, foscanet, and cidofovir are the agents available to slow the progression of CMV retinitis, but they have significant toxicities.

Scope of the problem

Although Hawaii is a relatively small state, the annual rate of acquired immunodeficiency syndrome (AIDS) of 16.7 per 100,000 people placed Hawaii at 19th among the 50 states and District of Columbia in 1996.1 The Hawaii Department of Health estimates that approximately 2,300 to 3,200 individuals infected with human immunodeficiency virus (HIV) live in the islands.2 This represents 0.25 percent of the population or one of every 400 persons.

Over 70% of patients with AIDS can develop ocular manifestations, and 90% of patients have ocular disease at autopsy.3 Diseases of the anterior segment of the eye include: molluscum contagiosum, Kaposi’s sarcoma, dry eyes, herpes zoster ophthalmicus, herpes simplex keratitis, and microsporidiosis. The retina and choroid can show involvement with “HIV retinopathy” (retinal hemorrhages, microvascular abnormalities, nerve fiber layer infarcts), cytomegalovirus (CMV), herpes simplex, herpes varicella-zoster, syphilis, toxoplasmosis, pneumocystis, cryptococcus, mycobacteria, histoplasmosis, candida, and endogenous bacterial retinitis.4 Vascular occlusions are possible.5 Loss of visual function on psychophysical testing without infectious retinopathy has been studied.6 Optic neuropathy, cranial nerve palsies, orbital lymphoma, and orbital infections can be seen.

Medications used to treat the HIV patient can result in ocular side effects. Rifabutin-associated iritis8 and Didanosine related retinal pigment epithelial atrophy have been reported.9

HIV retinopathy

The most common ophthalmoscopic finding is the microvascular changes of HIV retinopathy. The cotton-wool-spots (representing nerve fiber layer infarcts), hemorrhages, and microvascular changes do not represent an opportunistic infection. They are usually asymptomatic and will resolve spontaneously. For a patient with known HIV infection, they have no prognostic value and need only to be distinguished from an infectious lesion.

The differential diagnosis of cotton-wool-spots and hemorrhages is nonspecific, and includes: HIV retinopathy, diabetes, hypertension, collagen vascular disease, retinal vascular occlusions, carotid artery disease, anemia, high altitude retinopathy, dysproteinemias, leukemia, radiation, pancreatitis, and systemic infections.

CMV retinitis

The most common ocular infection and cause for visual loss is CMV retinitis which can affect up to 30% patients with AIDS.10 CD4+ T-cell counts are usually below 0.05 x 10⁹/L.11 Occasionally, CMV retinitis may be the presenting opportunistic infection. The patient may present with symptoms of floaters, flashing lights, a visual field defect, or blurred vision. The retinitis may also be discovered on a screening ophthalmoscopic examination. Lesions may be asymptomatic because they are small and in the peripheral retina, or an individual may not be paying attention to the sight in each eye separately.

The diagnosis of CMV retinitis is based on the clinical appearance of a focal necrotizing retinitis There are multiple, granular, white foci of retinal whitening with areas of confluence often with associated hemorrhage. The red and white appearance has been likened to that of a cheese pizza (Figure 1). A small area of retinitis may resemble a cotton-wool-spot, but a nerve fiber layer infarct will resolve in time. Untreated CMV retinitis spreads like a brush fire. Active, expanding borders leave behind atrophic retina and mottled retinal pigment epithelium.

Treatment of CMV retinitis

Medications against CMV approved by the Federal Drug Administration at this time are ganciclovir, foscanet, and cidofovir. All have been shown to effective in slowing the progression of retinitis. Successfully treated retinitis shows choriotretinal scarring with no active granular retinal whitening (Figures 2, 3). Fibroglial tissue, refractile particles, or white plaques can sometimes occur. The drugs are virostatic and must be taken indefinitely.

Ganciclovir was developed first, and therefore it has had the most use. This nucleoside analogue is available intravenously, orally, or as an implant into the vitreous cavity. The Hawaii AIDS Clinical
Research Program (HACRP) with participating local ophthalmologists was involved in two of the clinical trials involving oral ganciclovir (Syntex ICM 1653 and ICM 1774). The intravenous and oral form should be taken daily for maximal efficacy. Bone marrow suppression is a major side effect. The intravitreal implant involves an operation to suture a sustained-release device into the vitreous cavity. The drug diffuses through a polyvinyl alcohol coating and is effective for five to eight months. Systemic toxicity is avoided, but there is no treatment outside the eye or prophylaxis for the fellow eye.

Foscarnet is administered intravenously also on a daily basis. Infusion times are more lengthy than ganciclovir to avoid the side effects of renal toxicity and metabolic shifts.

Cidofovir is the most recently available agent. It has the advantage of having a maintenance schedule of an intravenous infusion once every two weeks. Probenecid is used to help decrease the nephrotoxicity. Ocular hypotony is possible.

Relapse of CMV retinitis after initial response to an anti-CMV medication is common and drug testing is measured by median time to progression (50 days for intravenous ganciclovir\(^\text{2,9}\), 93 days for foscarnet\(^3\), 120 days for cidofovir\(^4\), 226 days for the ganciclovir implant\(^5\)). Reinduction with the same drug or switching to another agent may again slow the retinitis. Combination treatment may be effective, but the trade-off is an increase in drug toxicities. Additional drugs are under investigation. Physicians in this state through the HACRP were involved with MSL 109 which is a monoclonal antibody against CMV. This study was terminated in 1997 due to preliminary data showing lack of efficacy and possibly increased mortality.

Retinal detachment is a serious complication of CMV retinitis. In one study, 24% of patients with CMV retinitis for one year developed a retinal detachment.\(^6\) Active retinitis and larger lesions are associated with a higher risk for detachment. The patient notices an abrupt shadow and loss of sight. With extensive areas of atrophic retina, a standard scleral buckling operation is usually not successful. Surgical treatment with the techniques of vitrectomy and silicone oil injection are needed to help reposition the retina and preserve sight.

**Other important causes of retinitis**

Toxoplasmosis causes a focal necrotizing retinitis in immunocompetent individuals and can also present in the patient with HIV infection. Clinically, toxoplasmosis has more inflammation in the vitreous and less hemorrhage than CMV retinitis. In the immunocompromised patient, the infection may be more fulminant making differentiation from CMV more difficult. The distinction is important because of the different treatment options which include pyrimethamine, sulfadiazine, clindamycin, folinic acid, and prednisone.

Acute retinal necrosis is a severe, rapidly spreading, necrotizing retinitis with vitritis, occlusive vasculitis, and optic neuritis caused by herpes zoster or simplex developing in an otherwise healthy individual. In the patient with AIDS, it may present with no vascular occlusion and minimal intraocular inflammation. This has been given the name progressive outer retinal necrosis (PORN).\(^7\) The rapid progression helps distinguish this infection from CMV retinitis. Prompt treatment with intravenous acyclovir is recommended.
but sight can still be abruptly and permanently lost. There is a high rate of retinal detachment.

**Screening**

Studies have shown that the risk of CMV is inversely related to the CD4+ T-cell counts. Some experts have used those counts to establish the frequency ophthalmologic examinations as follows: yearly for CD4+ T-cell counts greater than 0.10 x 10^9/L, every 6 months for CD4+ T-cell counts between 0.1 and 0.05 x 10^9/L, and every 4 months for CD4+ T-cell counts less than 0.05 x 10^9/L.

**Summary**

Ocular manifestations of AIDS are not uncommon in Hawaii. Most of the conditions mentioned above have been seen in Honolulu. The goal of the ophthalmologist is to maintain useful sight in an illness which has a high mortality. With early diagnosis of ocular diseases, this has been the case. Improved systemic treatment including new combinations of anti-HIV medications have prolonged the lives of many patients with AIDS. The challenge to preserve sight and decrease the ocular morbidity of AIDS continues to evolve with novel presentations of known diseases, new conditions, and advances in treatment modalities.

**References**