CHAPTER 13

Ocular Involvement in HIV Infection and AIDS

Highlights

- AIDS causes a microangiopathy known as *HIV retinopathy* that is associated with higher viral loads and lower $CD4^+$ T lymphocyte counts.
- Uveitis due to opportunistic infections—such as cytomegalovirus (CMV) retinitis, *Pneumocystis jirovecii* choroiditis, and *Cryptococcus neoformans* choroiditis—has become less common since the introduction of antiretroviral therapy.
- Immune recovery uveitis is sterile intraocular inflammation that develops after CMV retinitis when antiretroviral therapy improves the T-lymphocyte count.
- Malignant neoplasms such as vitreoretinal lymphoma and Kaposi sarcoma are associated with AIDS.

Acquired Immunodeficiency Syndrome

AIDS is caused by HIV, which infects and depletes $CD4^+$ helper T lymphocytes. The loss of $CD4^+$ T lymphocytes causes profound immune deficiency with subsequent opportunistic infections. See BCSC Section 1, *Update on General Medicine,* for a full discussion of HIV infection and AIDS.

Ophthalmic Manifestations

Ophthalmic manifestations may be the first sign of disseminated systemic HIV infection/AIDS and have been reported in up to 70% of infected people. These manifestations include

- HIV-related microangiopathy of the retina
- opportunistic viral, bacterial, parasitic, and fungal infections
- Kaposi sarcoma of the eyelid and conjunctiva
- lymphomas involving primarily the retina and/or vitreous (vitreoretinal lymphoma), adnexal structures, and orbit
- squamous cell carcinoma of the conjunctiva

Reports also suggest that HIV infection itself may cause anterior or intermediate uveitis that is unresponsive to corticosteroids but improves with antiretroviral therapy (ART).

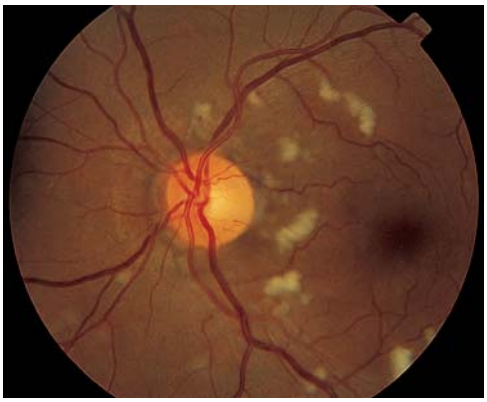

Figure 13-1 HIV retinopathy. Fundus photograph shows numerous cotton-wool spots. *(Reproduced with permission from Cunningham ET Jr, Belfort R Jr.* HIV/AIDS and the Eye: A Global Perspective. *Ophthalmology Monograph 15. American Academy of Ophthalmology; 2002:55.)*

The most common ocular finding in patients with AIDS is HIV retinopathy, a microangiopathy characterized mainly by cotton-wool spots (Fig 13-1) but also by microaneurysms and retinal hemorrhages. HIV has been isolated from the human retina, and its antigen has been detected in retinal endothelial cells. The HIV endothelial infection may play a role in the development of cotton-wool spots and other vascular alterations. In addition, accelerated aging may be a part of AIDS-associated eye disease, with earlier onset of macular degeneration and cataracts.

Other infectious agents that can affect the eye in patients with AIDS include cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), *Toxoplasma gondii, Treponema pallidum, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Cryptococcus neoformans, Pneumocystis jirovecii, Histoplasma capsulatum, Candida* species, molluscum contagiosum virus, and microsporidia. These pathogens can infect the ocular adnexa, anterior segment, or posterior segment. However, visual morbidity occurs primarily with posterior segment involvement, particularly retinitis caused by infection with CMV, HSV, VZV, *T gondii,* or *T pallidum.*

Agarwal A, Invernizzi A, Acquistapace A, et al; OCTA Study Group. Analysis of retinochoroidal vasculature in human immunodeficiency virus infection using spectral-domain OCT angiography. *Ophthalmol Retina.* 2017;1(6):545–554.

Kalyani PS, Fawzi AA, Gangaputra S, et al; Studies of the Ocular Complications of AIDS Research Group. Retinal vessel caliber among people with acquired immunodeficiency syndrome: relationships with visual function. *Am J Ophthalmol.* 2012;153(3):428–433.

Peters RPH, Kestelyn PG, Zierhut M, Kempen JH. The changing global epidemic of HIV and ocular disease. *Ocul Immunol Inflamm.* 2020;28(7):1007–1014.

Cytomegalovirus Retinitis

Before the availability of potent antiretroviral treatment regimens, disseminated CMV infection was the most common opportunistic infection in people with AIDS, and retinal infection was its most clinically important manifestation, occurring in up to 40% of patients with AIDS, usually those with $CD4^+$ T-lymphocyte counts less than 50 cells/μL. CMV infection is now uncommon in areas of the world where potent combination ART is available. However, CMV retinitis remains the most common opportunistic ocular infection in patients with

AIDS, and it is occasionally the first AIDS-defining infection diagnosed. CMV infection remains an increasing problem in resource-limited regions, particularly in Southeast Asia.

Early CMV retinitis may manifest as a small, white retinal infiltrate that resembles the cotton-wool spots seen in HIV-associated retinopathy. However, unlike HIV-associated retinopathy, CMV retinitis progresses without treatment. Patients with $CD4^+$ cell counts less than 50 cells/μL should be monitored every 3 months for development of CMV retinitis because it can be asymptomatic. In patients whose disease is not responding to therapy, polymerase chain reaction (PCR) testing of aqueous or vitreous fluids may help differentiate CMV from necrotizing retinitis secondary to HSV-1, HSV-2, or VZV infection. Of note, toxoplasmosis and syphilis may masquerade as a viral retinitis.

Management of CMV retinitis requires anti-CMV therapy and measures to restore immune function. Anti-CMV therapy is particularly important, as CMV retinitis signifies a twofold-increased mortality risk in patients with a $CD4^+$ T-cell count less than 100 cells/μL (an effect not observed with counts ≥100 cells/μL). Resistant CMV infection is further associated with increased mortality in patients with HIV infection/AIDS and CMV retinitis. Options for systemic coverage include high-dose induction therapy with either intravenous ganciclovir (5 mg/kg twice daily) or foscarnet (90 mg/kg twice daily) for 2 weeks, followed by maintenance therapy with daily dosing of either antiviral; or oral valganciclovir (900 mg twice daily) for 3 weeks, followed by maintenance therapy (900 mg/day).

Intraocular disease is treated effectively with intravitreal injection of ganciclovir or foscarnet (see Appendix B). In patients with vision-threatening retinitis, intravitreal injection may be used as an adjunct to systemic antiviral treatment (Fig 13-2). Intravitreal treatment may be the only treatment option in patients who cannot tolerate systemic therapy because of myelotoxicity from valganciclovir or ganciclovir or because of nephrotoxicity associated with foscarnet.

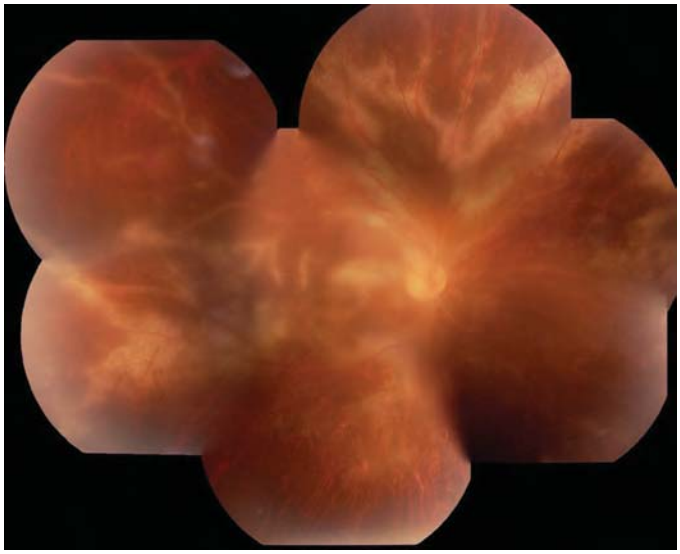

Figure 13-2 Cytomegalovirus retinitis. Montage of color fundus photographs shows diffuse retinitis with "frosted-branch" angiitis in a patient with AIDS. *(Courtesy of Emilio M. Dodds, MD.)*

HIV-infected patients with CMV retinitis who have sustained immune recovery (ie, $CD4^+$ T-lymphocyte count ≥100 cells/μL for 3–6 months) can safely discontinue systemic anti-CMV maintenance therapy. ART-naive patients may require only 6 months of anti-CMV therapy if they have good immune reconstitution, whereas ART-experienced patients may require long-term maintenance therapy. Despite immune recovery, patients with a history of CMV retinitis who discontinue anti-CMV maintenance therapy remain at risk for recurrence and should be monitored at 3-month intervals.

Ford N, Shubber Z, Saranchuk P, et al. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review. *Clin Infect Dis.* 2013;57(9):1351–1361.

Holland GN, Vaudaux JD, Shiramizu KM, et al; Southern California HIV/Eye Consortium. Characteristics of untreated AIDS-related cytomegalovirus retinitis. II. Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol*. 2008;145(1):12–22.

Jabs DA, Martin BK, Forman MS; Cytomegalovirus Retinitis and Viral Resistance Research Group. Mortality associated with resistant cytomegalovirus among patients with cytomegalovirus retinitis and AIDS. *Ophthalmology.* 2010;117(1):128–132.

Jabs DA, Van Natta ML, Holland GN, Danis R; Studies of the Ocular Complications of AIDS Research Group. Cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome after initiating antiretroviral therapy. *Am J Ophthalmol.* 2017;174:23–32.

Immune recovery uveitis

Immune recovery uveitis (IRU) is an inflammatory process that affects patients with a history of CMV retinitis and AIDS whose immune status improves with ART. The risk factors for developing inflammation depend on the extent of CMV retinitis (CMV retinitis surface area of 25% or more), amount of intraocular CMV antigen, degree of immune reconstitution, and previous treatment (higher risk in patients treated with cidofovir). Manifestations of IRU include anterior uveitis, vitritis, uveitic macular edema, epiretinal membrane formation, papillitis, and neovascularization of the optic disc or retina.

Inflammation in the anterior chamber is treated with topical corticosteroids. When IRU is an isolated mild vitritis, treatment is observation, as the vitreous inflammation can be transient. IRU with more severe vitreous inflammation and/or uveitic macular edema can be treated with periocular corticosteroids or short courses of oral corticosteroids. Intravitreal corticosteroids can also be used for treatment of severe IRU or uveitic macular edema; however, reactivation of CMV retinitis may occur.

El-Bradey MH, Cheng L, Song MK, Torriani FJ, Freeman WR. Long-term results of treatment of macular complications in eyes with immune recovery uveitis using a graded treatment approach. *Retina.* 2004;24(3):376–382.

Kempen JH, Min YI, Freeman WR, et al; Studies of Ocular Complications of AIDS Research Group. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology*. 2006;113(4):684–694.

Urban B, Bakunowicz-Łazarczyk A, Michalczuk M. Immune recovery uveitis: pathogenesis, clinical symptoms, and treatment. *Mediators Inflamm*. 2014;2014:971417. doi:10.1155/2014/971417

Retinal detachment

Retinal detachment occurs in up to 50% of patients with AIDS and CMV retinitis and may develop during active disease or after successful treatment of the retinitis. With potent

antiretroviral regimens available, the rate of retinal detachment has been reduced to 0.06 per patient-year. Risk factors for developing retinal detachment include involvement of all 3 retinal zones, lower $CD4^+$ T-lymphocyte count, and more extensive retinitis. Because eyes with CMV retinitis have extensive retinal necrosis and multiple posterior holes, most of these detachments require pars plana vitrectomy with long-term silicone oil tamponade. Anatomical reattachment can be achieved in 90% of patients.

Jabs DA, Van Natta ML, Thorne JE, et al; Studies of Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology*. 2004;111(12):2232–2239.

Necrotizing Herpetic Retinitis

Patients with HIV infection may develop necrotizing herpetic retinitis, which appears to manifest as a spectrum of disease; the severity is directly proportional to the degree of immunologic compromise. These patients may develop typical acute retinal necrosis or progressive outer retinal necrosis (PORN; see Chapter 12). In its early stages, PORN may be difficult to distinguish from peripheral CMV retinitis (Fig 13-3).

Wons J, Kempen J, Garweg JG. HIV-induced retinitis. *Ocul Immunol Inflamm.* 2020;28(8): 1259–1268.

Toxoplasma Retinochoroiditis

In immunocompetent patients, ocular toxoplasmosis classically appears as a focal retinochoroiditis often adjacent to a retinochoroidal scar. In patients with AIDS, it may be more difficult to diagnose ocular toxoplasmosis because of manifestations that differ from the classic presentation. For example, the ocular toxoplasmosis lesions are larger, and bilateral

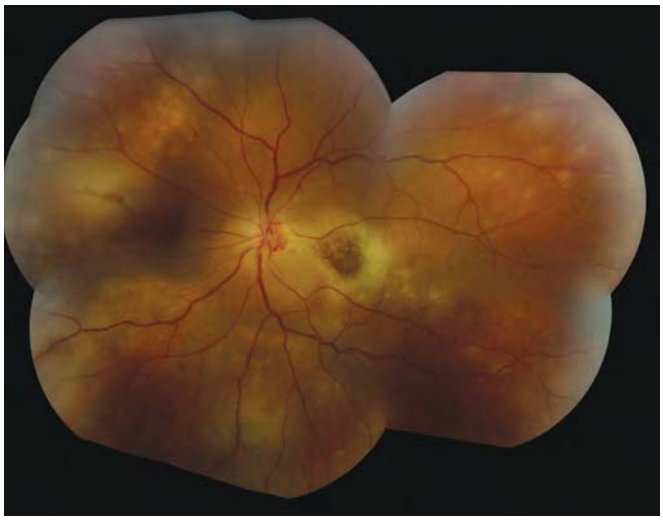

Figure 13-3 Progressive outer retinal necrosis. Montage of color fundus photographs shows extensive retinitis with relative preservation of vessels and early involvement of the posterior pole in a patient with AIDS. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

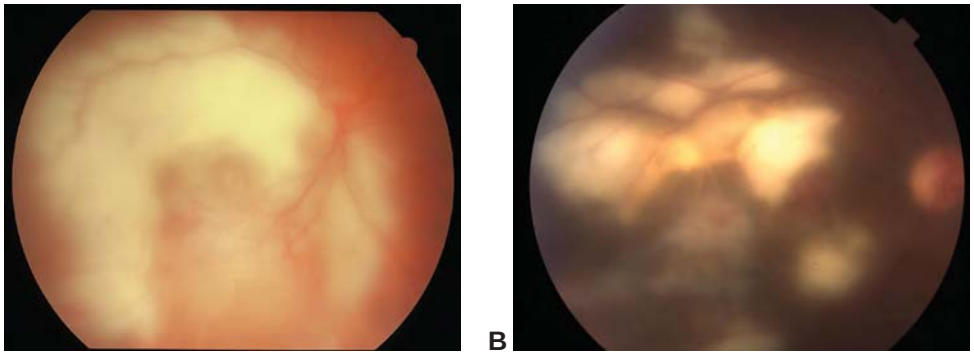

Figure 13-4 *Toxoplasma* retinochoroiditis. **A,** Fundus photograph shows a large area of macular *Toxoplasma* retinochoroiditis in a patient with AIDS. **B,** Fundus photograph from a different patient with AIDS demonstrates multifocal *Toxoplasma* retinochoroiditis. *(Courtesy of Emilio M. Dodds, MD.)*

disease occurs in up to 40% of cases. Solitary or multifocal patterns of retinitis have also been observed in these patients (Fig 13-4). In general, the inflammation in the choroid, retina, and vitreous is less prominent in patients with AIDS than in immunocompetent patients (see also Chapter 12). Also, trophozoites and cysts can be found in greater numbers within areas of retinitis, and *T gondii* organisms are occasionally seen invading the choroid, a finding not observed in immunocompetent patients.

Ocular toxoplasmosis may result from newly acquired *T gondii* infection or from reactivation of chronic infection within the retina or nonocular sites. In patients with AIDS, newly acquired *T gondii* infections and dissemination from nonocular sites are the most likely causes, although reactivation of quiescent toxoplasmosis also occurs. Thus, the retinochoroidal scars that are commonly associated with the active lesions of *Toxoplasma* retinochoroiditis may be absent. Further, ocular toxoplasmosis in patients with AIDS may be difficult to distinguish from acute retinal necrosis, necrotizing herpetic retinitis, or syphilitic retinitis. Definitive diagnosis may require aqueous and vitreous samples for culture and PCR analysis.

The prompt diagnosis of ocular toxoplasmosis is especially important in patients who are immunocompromised because the condition inevitably progresses if left untreated. In addition, ocular toxoplasmosis in these patients may be associated with cerebral or disseminated toxoplasmosis, both of which are important causes of morbidity and mortality in patients with AIDS. For patients with AIDS who have active ocular toxoplasmosis, computed tomography and/or magnetic resonance imaging of the head, as well as consultation with specialists in infectious diseases should be pursued to rule out central nervous system (CNS) involvement (Fig 13-5).

Anti-*Toxoplasma* therapy with a synergistic combination of pyrimethamine, sulfadiazine, sulfamethoxazole and trimethoprim, azithromycin, atovaquone, and/or clindamycin is required. Because of the risk of further immunosuppression in this population, corticosteroids should be used with caution and only when there is appropriate antimicrobial coverage. In selecting the therapeutic regimen, the physician should consider the possibility of coexisting cerebral or disseminated toxoplasmosis as well as the toxic effects of pyrimethamine and sulfadiazine on bone marrow. Continued maintenance therapy may be necessary for patients with poor immune status that is not improving. See Chapter 12 for more detailed discussion of treatment.

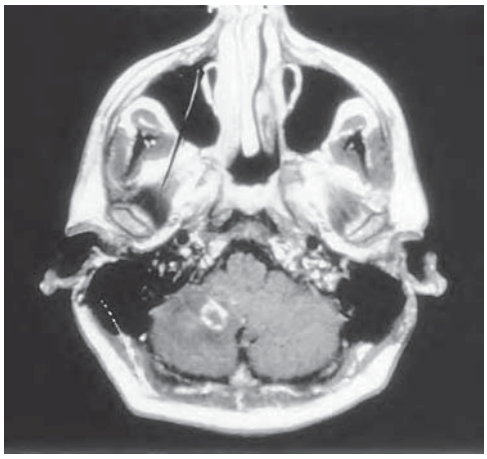

Figure 13-5 Central nervous system toxoplasmosis. Enhanced computed tomography scan reveals a cerebellar *Toxoplasma* lesion in a patient with AIDS who presented with ataxia. *(Courtesy of John D. Sheppard Jr, MD.)*

de-la-Torre A, Gómez-Marín J. Disease of the year 2019: ocular toxoplasmosis in HIV-infected patients. *Ocul Immunol Inflamm*. 2020;28(7):1031–1039.

Ocular Syphilis

Syphilis, which is due to *T pallidum* infection, is reemerging globally, particularly in association with HIV coinfection. The clinical presentation of ocular syphilis includes scleritis; anterior, intermediate, posterior, or panuveitis; and optic neuritis. Patients may also have mucocutaneous and CNS symptoms. In patients with AIDS, vitritis without chorioretinitis can be the first manifestation of syphilis. In contrast to patients without HIV infection, these patients are also more likely to present with optic neuritis or neuroretinitis. A classic manifestation of syphilis in patients with AIDS is unilateral or bilateral pale-yellow, placoid retinal lesions that preferentially involve the macula (syphilitic posterior placoid chorioretinitis). The presence of discrete creamy-yellow superficial retinal precipitates overlying areas of retinitis is very suggestive of syphilis; however, these precipitates can occur regardless of HIV status. For discussion of other manifestations of syphilis, see Chapter 11.

The course of syphilis may be more aggressive in HIV-infected patients. These patients require treatment with 18–24 million units of intravenous penicillin G administered daily for 10–14 days, followed by 2.4 million units of intramuscular benzathine penicillin G administered weekly for 3 weeks. Monitoring of results from the quantitative rapid plasma reagin test is recommended, as symptomatic disease can recur.

Queiroz RP, Smit DP, Peters RPH, Vasconcelos-Santos DV. Double trouble: challenges in the diagnosis and management of ocular syphilis in HIV-infected individuals. *Ocul Immunol Inflamm*. 2020;28(7):1040–1048.

Multifocal Choroiditis and Systemic Dissemination

The choroid is often a site of opportunistic disseminated infections. Multifocal choroidal lesions resulting from ocular infection are found in up to 10% of patients with AIDS; discovery of these lesions should prompt an exhaustive workup because they can be a sign of

disseminated infection. Common etiologic agents are *C neoformans, P jirovecii, M tuberculosis,* and atypical mycobacteria. Because of the profound immunosuppression in patients with AIDS, multiple infectious agents may cause simultaneous infectious multifocal choroiditis.

Pneumocystis jirovecii *choroiditis*

Patients with AIDS are at increased risk for *P jirovecii* pneumonia. In rare cases, this infection can result in a choroiditis with infiltrates that contain the microorganisms. The choroidal lesions are slightly elevated, plaquelike, and yellow white with minimal vitritis (Fig 13-6). On fluorescein angiography, these lesions tend to be hypofluorescent in the early phase and hyperfluorescent in the later phases. If disseminated *P jirovecii* infection is suspected, an extensive evaluation should be conducted by a specialist in infectious diseases.

Treatment of *P jirovecii* choroiditis involves a 3-week regimen of intravenous trimethoprim (20 mg/kg/day) and sulfamethoxazole (100 mg/kg/day) or pentamidine (4 mg/kg/day). Within 3–12 weeks after treatment, most of the yellow-white lesions disappear, leaving mild overlying pigmentary changes. Vision is usually not affected.

Cryptococcosis

Cryptococcus neoformans is a yeast found worldwide in high concentrations in soil and pigeon feces. Infection is acquired through inhalation of the aerosolized fungus. It has a predilection for the CNS and may produce severe disseminated disease in immunocompromised or debilitated patients. Although overall it remains an uncommon disease, cryptococcosis is the most common cause of fungal meningitis as well as the most frequent fungal eye infection in patients with AIDS. The fungus probably reaches the eye hematogenously; however, the frequent association of ocular cryptococcosis with meningitis suggests that direct extension of infection from the optic nerve may result in ocular infection. Ocular infections may occur months after the onset of meningitis or, in rare instances, before the onset of clinically apparent CNS disease.

Ocular findings associated with cryptococcal meningitis include optic nerve edema followed by optic atrophy. Other manifestations include nystagmus and cranial nerve palsies associated with diplopia, ptosis, and ophthalmoplegia.

The most frequent presentation of ocular cryptococcosis that is not directly related to meningitis is multifocal choroiditis (Fig 13-7). Associated findings include granulomatous anterior chamber inflammation, variable degrees of vitritis, vascular sheathing, exudative

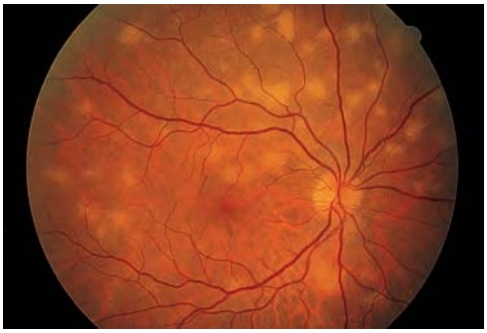

Figure 13-6 *Pneumocystis jirovecii* choroiditis. Fundus photograph shows multiple choroidal lesions. Findings were similar for the fellow eye. *(Reproduced with permission from Cunningham ET Jr, Belfort R Jr.* HIV/AIDS and the Eye: A Global Perspective. *Ophthalmology Monograph 15. American Academy of Ophthalmology; 2002:67)*

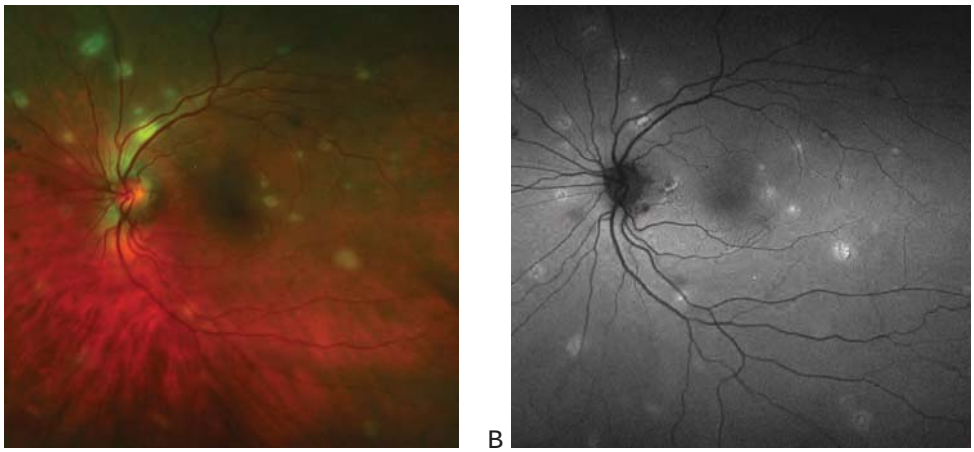

Figure 13-7 Cryptococcal choroiditis. Fundus photograph **(A)** and fundus autofluorescence image **(B)** show multifocal chorioretinal lesions. *(Originally published in the Retina Image Bank. Akshay S. Thomas, MD, MS. Retina Image Bank; 2018. Image number 28299. © American Society of Retina Specialists.)*

retinal detachment, and papilledema. It has been hypothesized that the infection begins as a focus in the choroid, with subsequent extension and secondary involvement of overlying tissues. Severe intraocular infection that progresses to endophthalmitis may occur in the absence of meningitis or clinically apparent systemic disease.

Diagnosis requires a high degree of clinical suspicion and is supported by demonstration of the organism with India ink stains or by positive *C neoformans* cultures of vitreous, chorioretinal biopsy specimens, or cerebrospinal fluid. Intravenous amphotericin B and oral flucytosine are required in order to halt disease progression. Systemic and intravitreal voriconazole may also be considered. With optic nerve or macular involvement, the prognosis for visual recovery is poor.

Aderman CM, Gorovoy IR, Chao DL, Bloomer MM, Obeid A, Stewart JM. Cryptococcal choroiditis in advanced AIDS with clinicopathologic correlation. *Am J Ophthalmol Case Rep.* 2018 Jan 31;10:51–54.

Kestelyn P, Taelman H, Bogaerts J, et al. Ophthalmic manifestations of infections with *Cryptococcus neoformans* in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol*. 1993;116(6):721–727.

Wykoff CC, Albini TA, Couvillion SS, Dubovy SR, Davis JL. Intraocular cryptococcoma. *Arch Ophthalmol.* 2009;127(5):700–702.

External Eye Manifestations

Other ophthalmic conditions associated with infection that occur in persons with AIDS include Kaposi sarcoma; molluscum contagiosum; herpes zoster ophthalmicus; and keratitis, which can be due to various viral or protozoal infections, conjunctival infections, and microvascular abnormalities. All of these conditions affect mainly the anterior segment of the globe and the ocular adnexa. These conditions are also discussed in BCSC Section 8, *External Disease and Cornea.*

Kaposi sarcoma

Human herpesvirus 8 is associated with Kaposi sarcoma. Two aggressive variants of this tumor have been described: an endemic variety especially prevalent in Kenya and Nigeria and a second variant, epidemic Kaposi sarcoma, which was first noted in renal transplant recipients and in patients with AIDS.

AIDS-associated Kaposi sarcoma may be found in visceral organs (the gastrointestinal tract, lung, and liver) in up to 50% of patients. Before the availability of potent ART, involvement of the ocular adnexa (orbit, eyelid, lacrimal gland, or conjunctiva) occurred in approximately 20% of patients with AIDS-associated systemic Kaposi sarcoma (Fig 13-8). Histologic investigation shows spindle cells mixed with vascular structures. Treatment of Kaposi sarcoma consists of excision, cryotherapy, radiotherapy, or a combination of these methods and is based on the clinical stage of the tumor as well as its location and the presence or absence of disseminated lesions.

Ong Beng Seng M, Meyer D, Gichuhi S, et al. Ocular surface disorders in patients with human immunodeficiency virus (HIV) infection. *Ocul Immunol Inflamm.* 2020;28(7): 1015–1021.

Molluscum contagiosum

Molluscum contagiosum is caused by infection with a poxvirus (family Poxviridae), which is a double-stranded DNA virus. The characteristic skin lesions are raised with central umbilication. In immunocompetent individuals, the eyelid lesions are few and unilateral. In contrast, in patients with AIDS, molluscum contagiosum eyelid lesions may be numerous and bilateral; if they are symptomatic or cause conjunctivitis, surgical excision may be necessary. These lesions may also resolve after ART.

Herpes zoster ophthalmicus

Herpes zoster ophthalmicus is caused by reactivation of latent VZV in the ophthalmic division of the trigeminal nerve. Testing for HIV should be considered for patients younger than 50 years who present with herpes zoster lesions of the face or eyelids. Corneal involvement can cause a persistent, chronic epithelial keratitis. Treatment consists of systemic and topical acyclovir. These patients should receive periodic monitoring with retinal examinations to ensure that posterior segment involvement does not occur.

Figure 13-8 Kaposi sarcoma. External photograph shows a hemorrhagic conjunctival tumor. *(Courtesy of Elaine Chuang, MD.)*

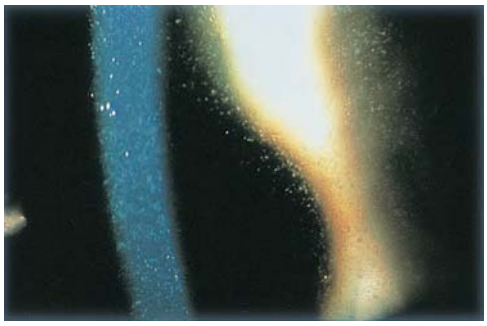

Figure 13-9 Microsporidia. Slit-lamp photograph of cornea shows punctate epithelial keratitis caused by microsporidia.

Other infections

Infection with HIV does not appear to predispose patients to bacterial keratitis, although bacterial and fungal keratitis can occur in patients with AIDS who have no obvious predisposing factors such as trauma or topical corticosteroid use. Infections can be more severe and are more likely to cause corneal perforation in patients with AIDS than in immunocompetent patients. Similarly, while patients with AIDS do not have a higher incidence of herpes simplex keratitis, they may have a protracted disease course or multiple recurrences, and the keratitis may involve the limbus. Microsporidial infection has been shown to cause a coarse punctate epithelial keratitis with minimal conjunctival reaction in patients with AIDS (Fig 13-9). Electron microscopy of epithelial scrapings has revealed the organism, which is an obligate intracellular parasite.

Solitary granulomatous conjunctivitis caused by cryptococcal or mycotic infection or by tuberculosis can occur in HIV-infected persons. Aggressive investigation for and treatment of dissemination, if present, is critical.