HIV/AIDS and the eye

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INTRODUCTION

The type of ocular involvement in the patient with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) depends on the level of immune function and systemic diseases present. Although the prognosis for patients with HIV/AIDS has changed dramatically with the introduction of antiretroviral therapy, infections involving the retina, such as toxoplasmosis, herpes simplex and herpes zoster (HZV), still occur although opportunistic infections such as cytomegalovirus (CMV) retinitis are much less common except in patients who present late in the course of the disease (Jabs and Bartlett, 1997; Jabs et al, 2002).

Identification of the ocular problem can sometimes help with the systemic diagnosis and therefore may have both sight and life-saving implications. In patients not yet on highly active antiretroviral therapy (HAART), assessment of the CD4 positive T-lymphocyte count and HIV viral load gives an indication of the level of immune dysregulation. CD4 cell count in particular is closely related to the risk of opportunistic infections and other problems that the patient may be susceptible to (Crowe et al, 1991; Masur et al, 2002). Immune reconstitution following HAART provides new opportunities in the treatment of ocular infections but may cause inflammation inside the eye.

PHASES OF HIV INFECTION

High CD4 count >500 cells/μl

HIV infection has different phases and the types of diseases seen depend on the functioning of the immune system. In the early phase the CD4 counts are usually >500 cells/μl. This phase can last several years, and the ocular diseases reflect dysregulation of the immune system rather than immunodeficiency, with autoimmune disease a feature. The clinical spectrum includes allergic conjunctivitis, Sjögren's syndrome, Reiter's syndrome, intraocular inflammation including retinal vasculitis, HIV microvasculopathy and optic neuropathy.

HIV microvasculopathy can occur at all stages of immune function and is thought to be a result of HIV infection of the retinal vascular cells. It rarely causes visual symptoms and consists of haemorrhages, microaneurysms and cotton wool spots, occurring predominantly in the posterior pole around the optic disc and macula (*Figure 1*). The haemorrhages come and go and the cotton wool spots break up over a period of a few weeks and re-occur in different sites. Histologically there is vascular pericyte drop out and basement membrane thickening, very similar to that seen in diabetic retinopathy although why this should be so is unknown.

Intermediate CD4 count 200–500 cells/μl

In this phase, there is some reduction of the CD4 count and increased susceptibility to a wide range of infections which may be the presenting problem. Ocular involvement can occur with a variety of infections including those caused by bacteria, fungi, viruses and parasites. Bacterial infection includes diseases such as conjunctivitis and blepharitis (infection of the lids) which can occur in anybody but may be more severe or refractory to treatment in HIV infection. Syphilis can cause intraocular inflammation (uveitis) and also a necrotizing retinitis.

Molluscum contagiosum are common and can occur on the eyelids. Molluscum, however, are rarely severe unless the CD4 count falls to less than 100 cells/μl. Herpes simplex virus can cause keratitis which may be difficult to treat, recurrences are common and vision may be lost if the centre part of the cornea is involved. HZV ophthalmicus involving the first division of the trigeminal nerve can cause severe lid infection and necrosis, severe intraocular inflammation with marked vitritis obscuring the retina and necrotizing retinitis (acute retinal necrosis, which may also be caused by herpes simplex virus) (*Figure 2*).

All necrotizing retinitis, whatever the cause, can lead to retinal detachment and loss of vision. In addition cerebral vasculitis can occur and cranial nerve palsies in the sixth (*Figure 3*) and third nerves may result. Patients are treated with intravenous aciclovir (oral therapy does not achieve a therapeutic level in the eye) to help prevent bilateral disease and laser treatment is given to try

Figure 1. Human immunodeficiency virus microvasculopathy – multiple cotton wool spots.

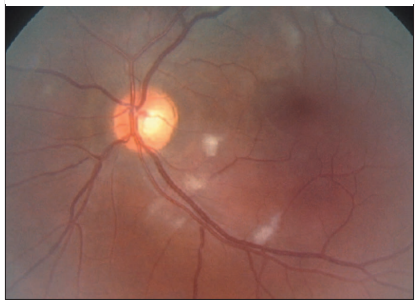
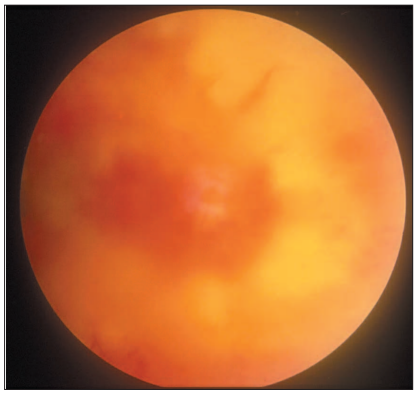


Figure 2. Acute retinal necrosis.



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and prevent retinal detachment occurring. Tuberculosis may be a problem in this group and can cause uveitis as well as choroidal granulomas which may be single or multiple (*Figure 4*).

Low CD4 cell count

At this stage the patient is susceptible to a wide range of infections including opportunistic infections and also to malignant disease. Patients whose CD4 count is <50 cells/μl may remain susceptible despite an initial response to HAART. Ocular manifestations include retinitis (CMV, toxoplasmosis, HZV), choroiditis (candida, pneumocystis, cryptococcosis, tuberculosis), and tumours (Kaposi's sarcoma, lymphoma).

Patients with *Mycobacterium avium intracellulare* (MAI) infection may receive rifabutin. Clarithromycin and fluconazole block the hepatic metabolism of rifabutin and high levels of rifabutin may accumulate in the eye resulting in profound loss of vision. The eye looks as if it is infected with bacteria with an intense inflammatory response that quickly quietens with topical steroids, rifabutin dose reduction or discontinuation of the additional agents (Tseng and Walmsley, 1995).

Figure 3. Herpes zoster ophthalmicus and sixth nerve palsy.

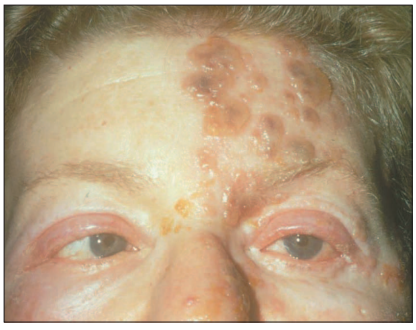
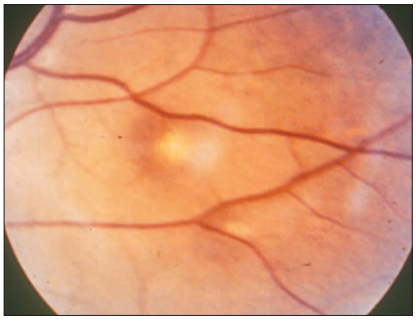


Figure 4. Choroidal tubercles.

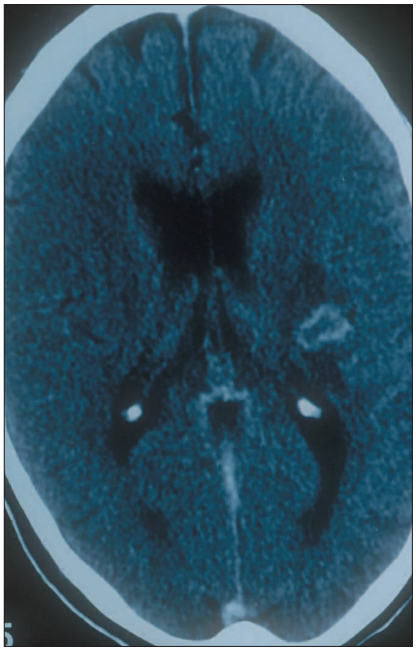


TOXOPLASMA

Toxoplasma retinitis in AIDS patients appears more frequently when the CD4 count falls below 150 cells/μl. As reported by Corchereau-Massin et al (1992), infection may be primary (positive immunoglobulin M), reactivation of previous ocular infection (based on the finding of old chorioretinal scars), or metastatic from another part of the body. Risk is greatest in patients from countries in whom prevalence of toxoplasmosis is high and who are seropositive reflecting past toxoplasma infection.

All HIV positive patients with a CD4 count of less than 200 cells/μl should be given be given prophylactic antibiotics to prevent *Pneumocystis carinii* infection. Sulphonamide antibiotics such as co-trimoxazole (septrin) used for this purpose also afford protection against toxoplasmosis. The clinical appearance varies and may be a focal necrotizing retinitis or diffuse or multifocal lesions. The degree of ocular inflammatory signs such as anterior uveitis and vitritis varies but are usually present (Gagliuso et al, 1990). There is a significant association of ocular toxoplasmosis with cerebral lesions (*Figure 5*) and thus a computed tomography brain scan is mandatory.

Figure 5. Computed tomography scan showing toxoplasma ring lesion in brain.



Patients with cerebral lesions may have papilloedema and/or sixth nerve palsies. First-line therapy is with sulphadiazine plus pyrimethamine and if this is not tolerated then clindamycin plus pyrimethamine, azithromycin or atovaquone may be considered. Oral corticosteroids are not indicated for ocular toxoplasmosis complicating HIV. A trial of treatment may be given where the diagnosis is uncertain and reduction in ocular and CNS lesions on this treatment will most likely occur. Biopsy of cerebral lesions should be considered if there is no response after 2 weeks. Maintenance therapy (secondary prophylaxis) can be safely discontinued when immune recovery is achieved with a CD4 count greater than 200 cells/μl sustained for at least 3 months (Masur et al, 2002).

CYTOMEGALOVIRUS RETINITIS

In the pre-HAART era CMV was a common opportunistic infection, with retinitis accounting for 75–85% of CMV disease in these patients. The risk of developing CMV retinitis increased when the CD4 cell count declined to <50 cells/μl with the estimated incidence of 20%/year, as reported by Kupperman et al (1993). The infection required lifelong therapy which was virostatic not virocidal, with reactivation of retinitis and therefore continuing retinal destruction occurring despite continuous treatment (Holland and Shuler, 1992; Anonymous, 1996). Epidemological studies in patients on HAART (Holzer et al, 1998; Pellela et al, 1998) have shown a decline in the rate of specific opportunistic infections owing to immune restoration, with rates of CMV retinitis dropping by approximately 55%.

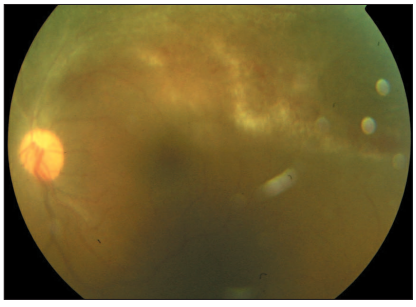
CMV infection results in full thickness retinal necrosis, which appears clinically as a white necrotic lesion with accompanied haemorrhages (*Figure 6*). In untreated patients there is little inflammation inside the eye whereas in patients on HAART in whom immune reconstitution is occurring there may be a profound inflammatory response which can induce vitritis and macular oedema, resulting in visual loss (Robinson et al, 2000).

Retinal detachment remains a problem in any eye infected with CMV and the risk increases with increasing destruction of the retina.

The mainstay of treatment is to try and induce immune recovery and a rise in CD4 count. This way the patient's own immune system controls the virus which is much more effective than current therapy. Patients with evidence of systemic CMV infection, for example a positive plasma polymerase chain reaction or CMV antigen, require systemic intravenous or oral anti-CMV therapy. Ocular disease is better managed with intraocular treatment, either with intravitreal ganciclovir or foscarnet, or a ganciclovir implant. Cidofovir may cause a uveitis particularly in patients on HAART and is less commonly used now (Rahhal et al, 1996; Davis et al, 1997; Ambati et al, 1999). Discontinuation of all anti-CMV therapy may be possible when the CD4 count rises to >100–150 cells/μl on HAART and is stable, as reported by Lin et al (2002).

Control of CMV within the eye is important to avoid immune reconstitution vitritis in which there is a vigorous inflammatory response to the virus and can be very difficult to treat as a good response to steroids may not occur (Karavellas et al, 2000, 2001). For this reason it is wise to evaluate high-risk patients (CD4 <75 cells/μl) for ocular CMV before initiating HAART. Inflammatory reactions following HAART have also been associated with diseases other than CMV retinitis, such as MAI infection with lymphadenopathy, pulmonary inflammation in tuberculosis and neurological deterioration in cryptococcal meningitis.

Figure 6. Cytomegalovirus retinitis: note the necrotic retinitis with haemorrhages.



HERPES ZOSTER VIRUS

In patients with very low CD4 counts, HZV can cause a fulminant outer retinal necrosis (previously known as progressive outer retinal necrosis or PORN but now called VZV retinitis) without vitritis in contrast to acute retinal necrosis which is usually associated with marked intraocular inflammation as described above. The retinitis starts as discrete lesions which rapidly coalesce and involve the central part of the retina. The disease is usually bilateral with early involvement of the second eye when uninvolved at presentation. Severe visual loss and retinal detachment occur within weeks, as reported by Batisse et al (1996) and Austin (2000).

VZV retinitis may, on occasion, be preceded by aseptic meningitis or retrobulbar optic neuritis (Franco-Paredes et al, 2002). Aggressive treatment is required, with combined intravitreal and high dose intravenous ganciclovir often combined with other drugs such as foscarnet. Treatment of retinal detachment requires intraocular surgery with vitrectomy and silicone oil tamponade, but the prognosis is poor.

SYPHILITIC RETINITIS

Syphilis and AIDS are epidemiologically associated. Ocular involvement of syphilis in AIDS patients is more aggressive and includes necrotizing retinitis with vitritis, retinal vasculitis, serous retinal detachment and neuroretinitis. The diagnosis is based on clinical presentation with positive serology. Treatment includes high-dose intravenous penicillin for 10–14 days.

INFECTIVE CHOROIDITIS

This is seen in patients with systemic infections and therefore indicates miliary spread. It can be seen in tuberculosis, fungal infection such as candidaemia, bacterial sepsis and pneumocystis. The widespread use of prophylaxis for *P. carinii*, and the introduction of HAART have contributed to the dramatic fall in the incidence of *P. carinii* choroiditis. The choroidal lesions are usually found on routine examination: one to several yellow-white lesions, located mostly in the posterior pole and up to the equator. Visual function is not compromised even if the lesion is under the fovea. The diagnosis is based on clinical presentation and bacteriological evidence based on other organ involvement particularly lung. The presence of pneumocystis in the choroid indicates the need for systemic rather than inhaled therapy and subsequent prophylaxis.

CRYPTOCOCCUS

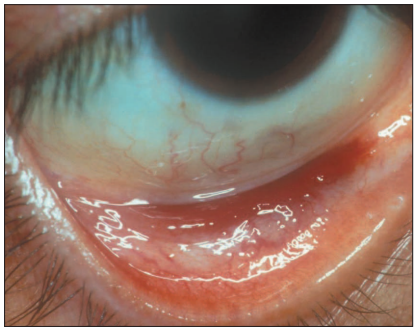
Ocular involvement in cryptococcal meningitis, which is a life-threatening infection in AIDS patients, is mainly related to papilloedema or optic neuropathy. Occasionally there are multifocal choroidal lesions similar to *P. carinii*, without anterior chamber or vitreal inflammation. First-line therapy for cryptococcal meningitis is intravenous amphotericin B combined with 5-flucytosine followed by fluconazole maintenance therapy (Saag, 2000).

TUMOURS

Kaposi sarcoma

Although this used to be fairly common in AIDS patients, its incidence has declined, as shown by Rutherford et al (1990). It has been strongly associated with human herpes virus type 8. The clinical appearance is of multicentric vascular red-purple nodules, which typically involve the skin. The ocular involvement includes the eyelids, the conjunctiva (*Figure 7*) (Kurumety and Lustbader, 1995) and rarely the lacrimal sac and the orbit. Spontaneous regression has been documented following HAART.

Figure 7. Kaposi sarcoma in lower lid.



Lymphoma

AIDS patients are at increased risk of developing non-Hodgkin's lymphoma as their life span increases, and are particularly at risk when their CD4 count has fallen below 50 cells/μl at any stage. The lymphoma is mostly of a high grade B cell type, and is associated with Epstein–Barr virus infection.

The most common presentation in the eye is from a primary CNS lymphoma with ocular involvement, and less frequently from spread to the eye by systemic lymphoma. Intraocular involvement of CNS lymphoma involves the vitreous and retina and may resemble viral retinitis, in contrast to systemic lymphoma, which more commonly spreads to the choroid, or presents as an orbital mass (Chan et al, 2002; Rivero and De Angelis, 1999). Treatment of lymphoma includes chemotherapy, with intrathecal methotrexate for CNS involvement (Nasir, 2000) and fractionated radiotherapy. Intravitreal methotrexate may be used for intraocular disease when recurrence occurs after radiotherapy but in general the prognosis is poor.

CONCLUSION

Assessment of an ocular problem in a patient with HIV/AIDS requires a knowledge of the patient's immune status, the other diseases they have or could have and the treatment that they are on. Although CMV retinitis has been reduced considerably in frequency in patients on HAART, many patients still present late and are at risk and other infective agents can also cause significant visual problems. The ocular signs may help with the differential diagnosis in an unwell patient. Close collaboration between the ophthalmologist and the HIV physician is essential in order to optimize patient care and prevent visual loss. HM

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