HIV and Ophthalmology

Although advances in medical therapy have reduced the number of lives lost to AIDS and the incidence of associated blinding infections, more subtle ocular manifestations are not uncommon.

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In the early 1980s, five homosexual men were admitted to the UCLA Medical Center in Los Angeles with *Pneumocystis carinii* pneumonia, mucosal candidiasis, multiple viral infections (including cytomegalovirus [CMV]), Kaposi's sarcoma, and a T-cell immune deficiency.[1] In 1982, Gary Holland, MD, then an ophthalmology resident at the Jules Stein Eye Institute at UCLA, published the first article describing the ocular manifestations of acquired immune deficiency syndrome (AIDS).[2] Dr. Holland's unique findings were instrumental in substantiating the internists' and infectious disease experts' impression that the patients were affected by a previously undescribed syndrome and were not just part of a cluster of individuals who had pneumocystosis, Kaposi's sarcoma, and other opportunistic infections.

A desire to learn more about the ocular manifestations of AIDS and to understand the pathogenesis underlying this newly recognized syndrome led to a fruitful collaboration between Dr. Holland, the late Robert Foos, MD (an ocular pathologist from UCLA), and Dr. Pepose, who had just completed an MD/PhD in virology in immunology at UCLA.[3,4]

Their initial studies defined the gamut of associated ocular infections, neoplasms, and vascular changes; explored the etiology of cotton-wool spots; and investigated the interaction of concurrent retinal infections with CMV, herpes simplex virus, and human immunodeficiency virus (HIV). They also studied the effects of antiviral therapy on CMV retinitis and the impact of the AIDS epidemic on corneal transplantation.

PREVALENCE OF HIV/AIDS

Looking back, it is hard to imagine that the small group of patients evaluated in Los Angeles in the early 1980s marked the start of an epidemic that has become the defining public health issue of our times. More than 1 million people in the United States are currently infected with HIV. Every year, more than 40,000 new cases of HIV infection are reported to the Centers for Disease Control, and over 33 million individuals carry the virus worldwide.

Men are more likely than women to contract AIDS, but the rate of HIV infection has been increasing among the latter group. In addition, racial and ethnic minorities in the United States appear to be affected by HIV disproportionately. Recent studies have shown that just over half the 1 million Americans living with AIDS are black and that HIV/AIDS represents the leading cause of death among black women between 25 and 34 years of age.[5]

Given these statistics, it is more important than ever for ophthalmologists to know how to recognize the ocular manifestations of HIV/AIDS.

THE EARLY EPIDEMIC

During the early years of the AIDS epidemic, researchers had little information about how the disease was transmitted between individuals. Because they did not know about HIV, they did not have a licensed screening test that could help them identify infected individuals. After researchers discovered HIV, they realized that a disease that first appeared to affect gay men primarily could also be transferred through:

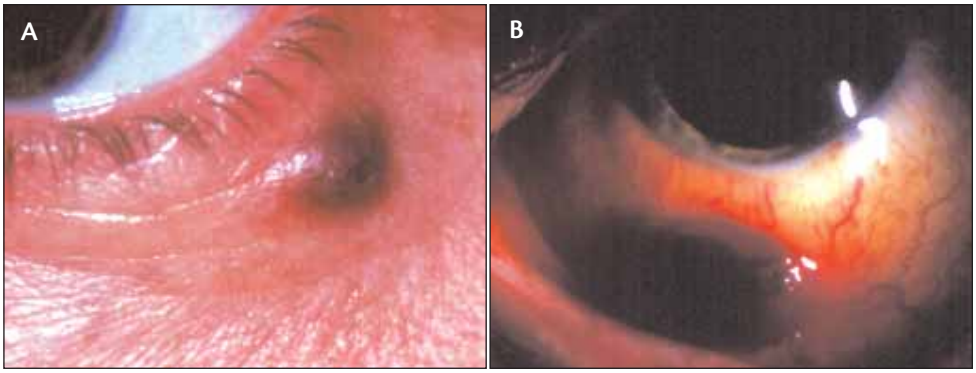

Figure 1. Kaposi's sarcoma on the eyelid (A) and conjunctiva (B) of a patient infected with HIV.

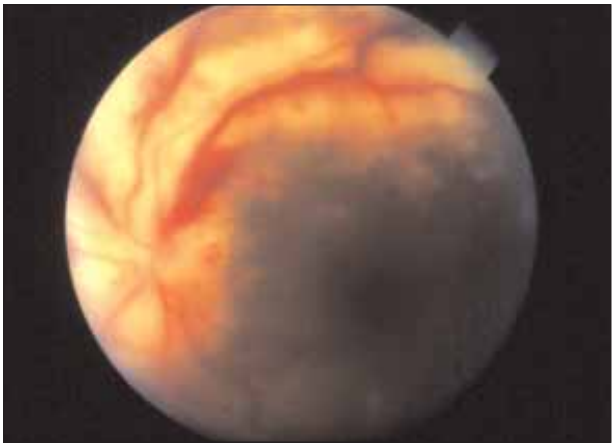

Figure 2. CMV can cause a catastrophic loss of vision in patients infected with HIV.

(1) Transfusion of blood and blood products
(2) Needlestick injury
(3) Abuse of intravenous drugs
(4) Heterosexual and homosexual intercourse
(5) Maternal transmission to neonates
(6) Transplantation of infected tissue and organs.

The risk of infection through corneal transplantation appears to be very low, however, because the current literature does not document any instances of transmission by this method.

Once researchers had identified HIV as the underlying cause of AIDS, they were able to develop reliable screening tests that could reduce the risk of transmission by the aforementioned methods. They also began studying the mechanism of viral replication in the hope that they could reduce patients' viral loads and therefore prevent or delay HIV-positive patients from progressing to AIDS. Investigators' first success came in the 1990s with the discovery of highly active antiretroviral therapy (HAART).

MANIFESTATIONS OF HIV/AIDS IN THE ERA OF HAART

HAART uses a combination of different potent antiretroviral drugs (including two reverse transcriptase inhibitors and a protease inhibitor) to suppress the replication of HIV. This drug regimen is generally associated with an initial increase in the number of helper T cells (CD4 count), fewer opportunistic infections and hospitalizations, and an increase in the length and quality of patients' lives.[4]

Prior to the introduction of HAART, patients often experienced a catastrophic loss of vision due to CMV retinopathy, herpes virus retinitis, and other infectious ocular diseases, including toxoplasmosis, syphilis, and cryptococcosis.[6] Patients who were affected by Kaposi's sarcoma sometimes developed the condition's characteristic raised red lesions on their eyelids or conjunctiva[7] (Figure 1). Kaposi's sarcoma was once a common manifestation of AIDS, but it is now seen less frequently.

Although HAART greatly reduced the prevalence and clinical severity of CMV retinitis in the United States, this ocular infection still occurs in HIV-positive patients, particularly those who have developed resistance to or toxicity from HAART, who have not been treated with HAART, or who already had CMV retinitis at the start of HAART therapy (Figure 2). In addition, some patients with CMV retinitis developed uveitis, epiretinal membranes, cystoid macular edema, vitritis, and visual loss following immune recovery associated with HAART therapy.[8]

MANIFESTATIONS OF HIV IN THE ANTERIOR SEGMENT

In 1992, a 22-year-old man with no known risk factors for HIV/AIDS died following a gunshot wound.[9] Although several postmortem tests were negative for HIV antibodies, the transplant patients who received his vascular organs and unprocessed fresh-frozen bone (but not his corneas) became HIV positive and eventually died from AIDS-related complications. Retrospective studies of the donor's cultured lymphocytes were positive for HIV-1, which led researchers to conclude that the donor had been infected with the virus shortly before his death but had not yet mounted an antibody response (the so-called *seronegative window*).

This tragic event highlights a number of safety issues of which we ophthalmologists should be aware. First, we must use universal precautions when examining all patients by disinfecting tonometers between uses, because human tears can harbor HIV and the viruses that cause hepatitis B and C. While performing fluorescein angiography, administering intraocular injections, and executing ocular surgery, we must take steps to prevent cross-contamination among patients and to limit the possibility of needlestick injuries. Finally, we should assume that all of the patients we see in the office or the OR may be infected with HIV, because many of them could be asymptomatic and thus unaware that they carry the virus.

In the era of HAART, patients infected with HIV are more likely to present with subtle visual disturbances than with catastrophic visual loss or severe retinal infections.[10] We should have an increased awareness of the potential loss of contrast sensitivity, visual field defects, and abnormalities in patients' color vision. These ocular findings do not seem to correlate with T-cell counts but may instead reflect the cumulative effect of HIV on different ocular structures.

For example, HIV may cause microvascular changes, alter blood flow to the retina, and induce focal ischemia in the retina or optic nerve. HIV-infected macrophages can cause additional damage to the optic nerve by triggering axonal

degeneration. These manifestations tend to become more prevalent with increasing age. Other common ocular conditions associated with HIV include dry eye syndrome and blepharitis. Occasionally, patients with a history of CMV retinitis whose immune systems have since been boosted by HAART may develop anterior uveitis along with the classic vitiritis of immune-recovery uveitis.

Although the introduction of HAART has reduced the incidence of molluscom contagiosum in patients infected with HIV, the anterior segment surgeon may encounter a variation of this viral infection characterized by multiple versus classic single lesions.[11] Molluscom contagiosum typically causes raised umbilicated masses on the eyelids that may shed virus into the conjunctiva. The result is a follicular conjunctivitis. Treatment involves curettage, cryotherapy, or excision. Likewise, the presence of herpes zoster in young people who otherwise are not likely develop this disease could be the first manifestation of immune deficiency.[12] Physicians may consider performing serological testing for HIV in patients under 50 years old, because they may be unaware that they may be infected with the virus. Immunocompromised patients are also at risk of developing associated severe pleomorphic dendritic epithelial keratitis, stromal keratitis, or anterior uveitis. If possible, these conditions should be treated with oral acyclovir or valcylovir within 72 hours of their onset in order to reduce the incidence of postherpetic neuralgia.

Physicians should always initiate antiviral therapy against the varicella zoster virus in immunocompromised patients, regardless of the time of onset. This intervention can reduce the incidence of the virus' cutaneous and visceral dissemination and the severity of ocular involvement.

THE FUTURE

HAART therapy is not a panacea for HIV/AIDS. It has, however, lengthened and improved the quality of the lives of individuals infected with the virus, many of whom succumb late in life to diseases that do not appear to be related to their HIV status.

Nevertheless, HIV continues to be a significant public health issue. The virus can mutate quickly in infected individuals. This ability has allowed HIV to acquire numerous mechanisms that help it to avoid the body's immune response and to develop resistance to antiviral therapy. Despite extensive efforts, researchers have yet to develop a much-needed, effective vaccine against HIV, and they are not likely to find one in the near future. It is to be hoped, however, that ongoing research will produce newer low-toxicity anti-HIV medications that more effectively reduce the viral loads of infected patients and prevent them from transmitting the disease to other individuals.

With 2.5 million new HIV infections reported annually worldwide, it is unlikely that we will be able to end this epidemic by only treating infected patients. Instead, our therapeutic efforts must be inexorably linked to programs for prevention and testing. Unfortunately, individuals in many developing countries and in some parts of the United States do not have ready access to HIV testing or antiretroviral therapy. In addition, efforts to educate the public about HIV have not effectively prevented the spread of the virus. We can therefore expect to see in these populations the same devastating ocular manifestations of HIV/AIDS that we observed during the first 10 years of the epidemic.

Ophthalmologists can do their part to prolong the lives of infected patients and decrease the risk of the virus' transmission by working with their colleagues in primary care and supporting global organizations that encourage HIV testing for patients at risk, provide pretest counseling, and improve access to affordable antiretroviral treatment. ❑

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