Role of HIV and CMV in the Pathogenesis of Retinitis and Retinal Vasculopathy in AIDS Patients

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Cotton-wool spots and cytomegalovirus (CMV) retinitis are seen frequently in AIDS patients. Human immunodeficiency virus (HIV) infection of the retina has been proposed as a mechanism for the high incidence of retinal pathology. An autopsy study of the eyes from 25 consecutive cases of AIDS was performed using gross examination, light microscopy, trypsin digestion of retinal vasculatures, and immunohistochemistry to evaluate the possible role of HIV, as well as CMV, in the pathogenesis of retinitis and retinal vasculopathy. Brain tissue was studied in the first 20 of these cases to evaluate any correlation between retinal and central nervous system pathology. CMV retinitis was observed in 15 cases (60%). Cotton-wool spots were seen in nine cases (36%). CMV encephalitis was detected in four cases, whereas HIV encephalitis was noted in five cases. We were unable to demonstrate a correlation between CMV retinitis and CMV encephalitis. However, the number of cases studied was small, and the frequency of CMV encephalitis was low. On the other hand, bilateral CMV retinitis demonstrated a correlation to HIV encephalitis \( (P < 0.005, \text{Fisher's exact test}) \). HIV infection of the retina was not detected by typical morphologic changes or immunohistochemistry. Immunohistochemistry localized CMV infection solely to areas of active retinitis. These findings suggest that bilateral CMV may serve as a marker of HIV encephalitis, possibly indicating a severely immunodepressed state. In addition, it appears that pathologically significant HIV infection of the retinal vascular endothelium that results in arteriolar occlusion or breakdown of the blood-retinal barrier does not occur frequently enough to account for the high incidence of cotton-wool spots and CMV retinitis seen in AIDS patients. Invest Ophthalmol Vis Sci 33:2345–2353, 1992

A wide variety of ocular lesions have been noted in patients with acquired immune deficiency syndrome (AIDS). The most common lesions are cotton-wool spots, which have been noted from 50 to over 70% of AIDS patients. Cytomegalovirus (CMV) is the most common infectious cause of progressive retinitis and is seen in 15–40% of AIDS patients.\textsuperscript{1–6} Several investigators have reported the identification of human immunodeficiency virus (HIV) in the retinas of AIDS patients and have speculated about a possible correlation between HIV infection of the retina and the pathogenesis of cotton-wool spots and CMV retinitis. Cultures of retinal tissue may be positive\textsuperscript{7,8} in some cases. However, HIV is present ubiquitously in leukocytes and the blood of AIDS patients, and studies using culture isolation are incapable of localizing HIV infection and are subject to possible contamination by infected leukocytes. Immunocytochemistry studies have shown variable results with staining that uses antibodies to some but not all HIV-related antigens.\textsuperscript{9–11} The frequency of HIV infection of neuronal and vascular elements of the retina remains to be elucidated, as does the role, if any, of HIV infection of the retina in clinically apparent disease.\textsuperscript{12}

Prior studies that employed immunocytochemistry showed mixed results regarding tissue localization and did not specifically look for the presence of HIV in or adjacent to cotton-wool spots. Because cotton wool spots result from vaso-occlusive events and because retinal infections are thought to result from breakdowns in the blood-retinal barrier, we performed an intensive study of retinal endothelium and retinal tissue. We specifically looked for infection associated with cotton-wool spots and retinal vascular endothelium as evidence of vascular endothelial involvement in the pathogenesis of retinal disease in AIDS. We studied the eyes of 25 patients who un-
nderwent autopsy examination at our institution to identify the presence of HIV and CMV in retinal and central nervous system (CNS) lesions and to correlate retinal and CNS disease. We performed immunohistochemical staining for CMV and HIV antigens on paraffin-embedded sections and also performed these studies on trypsin digest preparations of retinal vasculature. The paraffin-embedded sections allowed examination of structure and localization of specific antigens. Trypsin digest preparations allowed examination of expanses of retinal vasculatures in samples that made up one-fourth to one-third of the retina, providing thousands of endothelial cells for simultaneous inspection.

Materials and Methods

Each pair of eyes was obtained from 25 consecutive autopsies performed on AIDS patients who died at UCSD Medical Center (50 eyes total). CNS tissues were available from the first 20 of these cases.

Tissues were fixed in 10% buffered formalin for 3–7 d, then transferred to 50% ethanol until they were examined. Brains were examined for pathology, and a standard protocol was used so representative blocks from all areas were embedded in paraffin as previously described. Briefly, the brains were fixed for 1–2 wk in 20% formalin. Standard tissue blocks from the following CNS areas were paraffin embedded for histopathologic diagnosis: frontal cortex, caudate nucleus, insular cortex, basal ganglia, thalamus, hypothalamus, hippocampus, superior cerebellum, midbrain, pons, medulla, and spinal cord. To assess histopathologic changes, routine hematoxylin-eosin staining was performed on all of these blocks. Further examination under a dissecting microscope, and any lesions noted were diagrammed and photographed. An anterior segment of eyes selected for trypsin digestion was removed by incision immediately posterior to the ora serrata. The PO section then was vertically bisected through the optic disc, resulting in two rectangular peripapillary sections (a nasal portion and a slightly longer temporal portion containing the macula). Cut portions were immersed in water and the retina was gently dissected free. Retinal portions then were digested in a 3% phosphate-buffered trypsin solution for approximately 1 hr at 37°C. Digested sections then were prepared by dissecting free the internal limiting membrane and gently shaking the vessels free from digested tissue. Vessel preparations were flat mounted on organosilinated glass slides and allowed to dry at room temperature. Trypsin-digested vascular endothelial preparations from eyes with cotton-wool spots were taken from areas that contained these spots. Preparations from eyes with CMV retinitis contained vascular structures from normal areas posterior to areas of retinitis. Areas of active retinitis, as well as healed zones where the retina was atrophic and replaced by a thin glial membrane, dissolved during digestion and could not be processed.

Immunohistochemical staining for the immediate-early CMV antigen and the p24-HIV antigen by the avidin-biotin method was used on retinal tissues, brain tissues, and trypsin digest specimens as previously described. Mouse antiserum against human CMV at a dilution of 1:10 (Chemicon, Temecula, CA) and mouse antiserum against HIV p24 at a dilution of 1:10 (DuPont, Wilmington, DE) were used. After blocking of endogenous peroxidase and nonspecific immunoglobulin binding, sections were incubated with primary antibody for 2 hr at 37°C, then washed with phosphate-buffered saline. Sections then were incubated with biotinylated secondary antibody (goat anti-mouse IgG 1:50; Caltag, South San Francisco, CA) for 30 min at room temperature, followed by washing and incubation in an avidin horseradish peroxidase complex (Vector, Burlingame, CA) or an avidin alkaline phosphatase complex (Biogenics, San Ramon, CA). Reactions were developed with aminoethylcarbazole.

In eyes designated for embedding, the PO section was dehydrated and infiltrated with paraffin by standard histologic techniques, while the collettes were included if pathology was noted on gross examination. Blocks were step sectioned at approximately 600 μm increments. Several 5 μm sections were preserved from each step. One section from each step was stained with hematoxylin-eosin, while the remainder were preserved for other studies, such as immunohistochemical staining.

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CMV-infected and noninfected glial cells, as well as CMV-infected brain tissue, were used as controls for
CMV. HIV-infected and noninfected HUT-78 cells and HIV-infected brain tissue were used as HIV controls. Paraffin-embedded 10 μm thick sections of CMV- or HIV-infected brain tissue were used as controls for the trypsin digested vasculatures. These specimens were mounted on organosilanated glass slides, deparaffinized and rehydrated through a series of washings in xylene, alcohol, and water. They then were digested in 3% trypsin as previously described. All specimens were inspected by light microscopy.

For each run of immunocytochemical staining of paraffin- and trypsin-digested tissues, appropriate positive and negative control tissues were incorporated as outlined above.

### Results

The clinical and histopathologic findings of the 25 patients studied are summarized in Table 1. All patients were diagnosed with AIDS. Fifteen cases (22 eyes; 60%) had CMV retinitis. In all cases of retinitis, portions of the peripheral retina were involved, with

### Table 1. Systemic, retinal, and central nervous system (CNS) disorders

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age</th>
<th>Systemic disorders</th>
<th>Retinal findings</th>
<th>CNS findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>M</td>
<td>38</td>
<td>PCP, KS, CMV, and Candida esophagitis</td>
<td>CMV os</td>
<td>gliosis</td>
</tr>
<tr>
<td>2.</td>
<td>M</td>
<td>31</td>
<td>KS, PCP, thrush, CMV esophagitis</td>
<td>CMV ou</td>
<td>HIV encephalitis</td>
</tr>
<tr>
<td>3.</td>
<td>M</td>
<td>36</td>
<td>PCP</td>
<td>CWS ou</td>
<td>CMV encephalomyelitis</td>
</tr>
<tr>
<td>4.</td>
<td>M</td>
<td>41</td>
<td>PCP, herpes proctitis, *Pseudomonas* sepsis, chronic diarrhea, adenovirus pneumonia, CMV viremia and pneumonitis</td>
<td>CMV ou</td>
<td>lymphoma</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
<td>41</td>
<td>none</td>
<td>none</td>
<td>Toxoplasma encephalitis</td>
</tr>
<tr>
<td>6.</td>
<td>M</td>
<td>35</td>
<td>PCP, herpes keratitis, MAI bacteremia</td>
<td>CWS od</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>7.</td>
<td>M</td>
<td>32</td>
<td>Hepatitis B <em>Candida</em> esophagitis</td>
<td>CMV os</td>
<td>hepatic encephalopathy, CMV encephalitis</td>
</tr>
<tr>
<td>8.</td>
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<td>33</td>
<td>KS, PCP, CMV pneumonia</td>
<td>CMV os</td>
<td>chronic meningitis</td>
</tr>
<tr>
<td>9.</td>
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<td>39</td>
<td>pneumococcal sepsis, thrush, AFB bacteremia</td>
<td>CMV od</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>10.</td>
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<td>27</td>
<td>seizures, bronchopneumonia</td>
<td>CMV ou</td>
<td>chronic meningitis</td>
</tr>
<tr>
<td>11.</td>
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<td>45</td>
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<td>HIV encephalitis, Cryptococcal meningitis</td>
</tr>
<tr>
<td>12.</td>
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<td>CMV ou</td>
<td>none</td>
</tr>
<tr>
<td>13.</td>
<td>M</td>
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<td>PCP</td>
<td>none</td>
<td>HIV encephalitis, Cryptococcal meningitis</td>
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<tr>
<td>14.</td>
<td>M</td>
<td>39</td>
<td>PCP, KS</td>
<td>CMV od</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>15.</td>
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<td>none</td>
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<tr>
<td>16.</td>
<td>F</td>
<td>6</td>
<td>PCP, GI TB, CMV pneumonitis, <em>Candida</em> pneumonitis</td>
<td>CMV os</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>17.</td>
<td>M</td>
<td>47</td>
<td>Hodgkin's disease</td>
<td>CWS ou</td>
<td>chronic meningitis, gliosis</td>
</tr>
<tr>
<td>19.</td>
<td>M</td>
<td>33</td>
<td>PCP, CMV hepatitis, <em>Campylobacter</em> osteomyelitis</td>
<td>CMV ou</td>
<td>HIV encephalitis</td>
</tr>
<tr>
<td>20.</td>
<td>M</td>
<td>42</td>
<td>pulmonary AFB, thrush, hepatitis B, <em>Shigella</em></td>
<td>CWS od</td>
<td>HIV encephalitis, CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>21.</td>
<td>M</td>
<td>46</td>
<td>KS, toxoplasmosis, cryptococcal septicemia</td>
<td>CMV od</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>22.</td>
<td>M</td>
<td>31</td>
<td>CMV pneumonia, <em>Candida</em> sepsis</td>
<td>CWS os</td>
<td>CMV encephalitis, gliosis</td>
</tr>
<tr>
<td>23.</td>
<td>M</td>
<td>30</td>
<td>CMV pneumonia, KS, <em>Cryptococcal</em> pneumonia</td>
<td>CWS ou</td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>M</td>
<td>44</td>
<td>CMV colitis, MAI, PCP, <em>Clostridium</em> septicum bacteremia, group C beta Strep. bacteremia</td>
<td>CMV ou</td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>M</td>
<td>56</td>
<td>thrush, disseminated MAI, disseminated <em>Cryptococcus</em> lulleae, AFB, acid-fast bacilli, ITP, immune thrombocytopenia, GI TB, gastrointestinal tuberculosis</td>
<td>CWS ou</td>
<td></td>
</tr>
</tbody>
</table>

*Pneumocystis carinii* pneumonia. KS, Kaposi's sarcoma. CMV, cytomegalovirus. os, left eye. ou, both eyes. HIV, human immunodeficiency virus. CWS, cotton-wool spots. od, right eye. MAI, mycobacterium avium-intracellular.
extension progressing to include the posterior poles in seven cases (nine eyes). The retinitis had a characteristic appearance of a continuous spreading lesion, leaving behind an area of atrophic retina (Fig. 1).\textsuperscript{12,16-18} Cotton-wool spots were noted on gross examination in nine cases (14 eyes; 36%). Two eyes with cotton-wool spots had concurrent CMV retinitis, and two cases had CMV retinitis in the contralateral eye. The cotton-wool spots all occurred within 3 disc diameters of the optic disc and generally occurred adjacent to the vascular arcades. Eighty three sections through or adjacent to 14 cotton-wool spots from four eyes were identified and studied by light microscopy. No histologic evidence of cytomegalovirus, \textit{Pneumocystis}, \textit{Toxoplasmosis}, or fungal infection was noted in or adjacent to any cotton-wool spot. In addition, no inflammation by polymorphonuclear or mononuclear cell infiltrates was seen. Trypsin-digested vasculatures showed no cytomegalic endothelial cells or viral inclusions indicative of CMV infection, or multinucleated giant cells indicative of HIV infection (Fig. 2).

Immunohistochemical staining of paraffin-embedded sections for immediate early CMV antigen stained the leading active edges of retinitis (cases 10, 12, 14-16, 19-21), but did not stain in or adjacent to cotton-wool spots (37 sections from 11 cotton-wool spots; cases 17, 22, 23), or in areas of normal-appearing retina (Fig. 3). Immunohistochemical staining of trypsin digest preparations was attempted, but trypsin-digested control brain tissue from regions of CMV encephalitis did not stain for the immediate early antigen, indicating the digestion procedure destroyed this antigen.

Immunohistochemical staining for HIV p24 antigen was negative in all specimens. Specifically, no HIV antigen was detected in areas of CMV retinitis (cases 10, 12, 14-16, 19-21), cotton-wool spots (32 sections from 11 cotton-wool spots; cases 17, 22, 23), or retinal vascular endothelium (Fig. 4). Trypsin digest preparations from 12 cases (3, 10, 12, 14-17, 19, 20, 23-25) also did not stain for the p24 antigen. Trypsin digest preparations of control brain tissue with HIV encephalitis showed staining for p24 antigen in areas of multinucleated giant cells. However, staining was reduced when compared to brain sections that had not been extensively trypsinized (Fig. 5).

CMV encephalitis was noted in four cases by the presence of typical cytomegalic cells and immunohistochemical demonstration of viral antigen. However, only two of the four cases of CMV encephalitis also had CMV retinitis. HIV encephalitis was diagnosed.

Fig. 1. Paraffin-embedded section of cytomegalovirus retinitis stained with hematoxylin-eosin. A solitary focus of retinal infection with retinal necrosis flanked by morphologically normal retina. (x400.)
Fig. 2. Trypsin digest flat mount of retina stained with hematoxylin-eosin. The neural retinal structures have been digested away, leaving a network of retinal vascular endothelium and pericytes. No cytomegalic cells nor multinucleated giant cells are seen. (X200.)

Discussion

The present autopsy study of 25 cases of AIDS was designed to investigate the cause of AIDS-associated retinal vasculopathy, hallmarking by cotton-wool spots, and to determine the association, if any, between CNS and retinal infection with CMV and HIV. Cotton-wool spots occur in a variety of diseases, including AIDS, diabetes, hypertension, systemic lupus erythematosus, and anemia. These patches appear as small, white, superficial retinal opacities and generally occur in the posterior pole. Cytoid bodies form as the result of accumulation of neurofilaments and dense bodies in axons of the nerve fiber layer. This is thought to be the result of retinal ischemia from an infarction of a precapillary arteriole. Cotton-wool spots are transient and resolve over a 4-12 wk period. Areas of thickened and occluded capillaries, microaneurysms, and capillary dropout have been demonstrated by fluorescein angiography and trypsin digestion. The cause of potential vaso-occlusive events in the retina of AIDS patients is unclear. Direct infection of endothelial cells by HIV—as well as immunoglobulin deposition, circulating immune complexes containing HIV antigens, *Pneumocystis carinii*, alterations in hematologic factors, secretion of monokines, and proteolytic enzymes—all have been suggested as causes of cotton-wool spots in AIDS. Because numerous cotton-wool spots appear in close to 100% of AIDS patients during the course of the disease, evidence of HIV antigens and cytopathologic effects would be expected in retinas of AIDS pa-
Fig. 3. Paraffin-embedded section of cytomegalovirus (CMV) retinitis, immunostained for immediate early CMV antigens. Black nuclear inclusions (arrows) mark sites of nuclei containing CMV immediate early antigens. (Counterstained with hematoxylin, ×400.)

patients if these lesions occurred secondary to productive HIV infection.13

We observed cotton-wool spots in 36% of the autopsies. These were seen through inspection of flat mounted retinal tissue in paraffin sections. Areas of vascular change also were seen on trypsin digestion. These lesions, when still visible, represent recent (within 2–3 mo) arteriolar occlusion. Given the transient nature of cotton-wool spots, the actual number of such infarctions is undoubtedly much higher. The prevalence of vascular retinopathy in our study is likely greater than 75%. Despite the incidence of retinopathy in our series and the high incidence universally seen in AIDS patients, we were unable to detect the presence of HIV by immunohistochemistry in the retina. Areas of fresh cotton-wool spots were studied by immunohistochemistry in tissue sections, as were areas of CMV retinitis and normal appearing retina. Using the same fixation and immunohistochemical techniques, we have been consistently able to find HIV in the CNS in areas of multinucleated giant cells and macrophage infiltrates.15 In addition, all trypsin digest preparations stained for p24 were negative. The trypsinization procedure may have affected the p24 antigen, as it did for the CMV immediate early antigen. However, HIV-infected control brain tissue stained p24 antigen after treatment with trypsin, although at a less intense level. Therefore, HIV infection of the retinal vascular endothelium, if present, does not lead to detectable p24 antigen in these cells. While detection of the gag antigen p24 has been commonly used, it is not the most sensitive method for detecting HIV. Ongoing studies that employ the polymerase chain reaction should provide the theoretical sensitivity limit of single proviral copy detection. It is possible, however, that this very sensitive technique may be plagued by the detection of inconsequential amounts of virus (eg, blood contaminants) and may not help define a role for HIV in AIDS retinal pathology.

HIV antigens have been detected in retinal tissue by Pomerantz and associates, who suggested a localization of antigens in the retinal endothelium among other cell types.6 Schmitt-Graff and associates also were able to identify HIV in various layers of the retina. However, they were unable to detect HIV in the retinal vascular endothelium.11 In addition, Kennedy and coworkers were unable to detect HIV in the retina by in situ hybridization.26 In light of these various studies and our results, it appears that although HIV
infection of the retina may occur, it is not a consistent finding and has a questionable association with significant pathology.

The detection of HIV infection of the retina led to the hypothesis that HIV infection of the retinal vascular endothelium may be a causative factor in the development of the retinopathy of AIDS and in the breakdown of the blood-retinal barrier, leading to an increased occurrence of CMV retinitis. Although HIV may infect the retinal endothelium, our study, with other studies, indicates that this occurs only rarely and therefore does not account for the high incidence of retinopathy and CMV retinitis seen in AIDS patients. It is striking that cotton-wool spots probably occur universally in AIDS patients. In our study, we looked extensively at cotton-wool spots and trypanized retinal vasculatures for HIV infection evidenced by morphologic changes and immunohistochemistry. Therefore, cotton-wool spots probably do not occur secondary to productive HIV infection of the retina or the retinal vascular endothelium. In addition, our inability to detect evidence of CMV infection in or adjacent to cotton-wool spots supports earlier studies that indicate cytomegalovirus infection is not involved in the pathology of cotton-wool spots seen in AIDS patients.

In comparing CNS infections to retinal pathology, we were unable to find a correlation between CMV retinitis and CMV encephalitis within the limits of our study. However, although our numbers were small, bilateral CMV retinitis did correlate well with HIV encephalitis, as defined by the presence multinucleated giant cells or HIV-positive macrophages distributed in subcortical structures. Our findings contrast with an earlier study that suggested a correlation between CMV retinitis and encephalitis. However, the previous study was not intended to compare CNS and ocular pathology. In addition, that study consisted of patients who were not treated with anti-CMV drugs, whereas in our study only four of the cases with CMV retinitis were untreated, two of which were very early infections. These findings suggest that CMV retinitis in AIDS occurs by hematogenous spread rather than as an extension of CMV infection from the CNS through the optic nerve. It also appears that treatment of CMV retinitis may curtail CMV infection of the brain. The correlation between bilateral occurrence of CMV retinitis and HIV infection of the brain is as-
Fig. 5. Paraffin section of trypsin-digested brain tissue from a patient with HIV encephalitis, immunohistochemically stained for human immunodeficiency virus (HIV) gag protein p24 after trypsin digestion. A multinucleated giant cell in the center of the field shows a light cytoplasmic staining for HIV gag protein p24. Adjacent neuronal and glial cells do not stain. (Counterstained with hematoxylin, ×100.)

Fig. 6. Paraffin section of brain tissue from a patient with human immunodeficiency virus (HIV) encephalitis, immunohistochemically stained for HIV gag protein p24 without trypsin digestion. Perivascular mononuclear cells show cytoplasmic staining for HIV gag protein p24. Staining for p24 antigen is more intense without trypsin digestion, consistent with some loss of antigenicity. (Counterstained with hematoxylin, ×100.)

tounding. Bilateral CMV retinitis appears to be a marker for HIV infection of the brain. At least two explanations are possible. Bilateral CMV retinitis may indicate a severe immunodepressed state, which predisposes to infection of the brain with HIV. Alternatively, bilateral CMV retinitis may be a marker for disseminated CMV disease. Disseminated CMV disease and viremia with CMV may interact with HIV, allowing for productive HIV infection of the CNS. Given the small numbers in our study, these conclusions appear tenuous. On the other hand, further investigations may support these results.

Recently, the in vitro enhancement of CMV propagation by coinfection with HIV was demonstrated. 9 Dual infection of brain and retinal cells with CMV and HIV also has been reported. 10,29,36 These findings suggest the possibility of in vivo synergism between CMV and HIV. It is possible that a transient infection of the retina with HIV allows the retina to be seeded with CMV. However, it is important that we did not detect HIV in the retinas of eight eyes with CMV retinitis. Given the high incidence of CMV retinitis in AIDS patients and the inability to detect equivalent occurrences of retinal HIV infection, especially in areas of CMV, it appears unlikely that in vivo, productive HIV infection is responsible for enhancing CMV production in cases of retinitis.

Integrating our findings with those of others, we
believe that damage to the retinal endothelium that results in ischemic changes (ie, cotton-wool spots) or seeding of the retina with CMV that results in retinitis is not caused by direct retinal endothelial infection by HIV. Rather, some other process, perhaps immune complex deposition or local release of cytotoxic substances such as monokines or proteolytic enzymes, may be responsible. Further studies that use more sensitive technology, such as polymerase chain reaction, may be able to detect histopathologically important HIV infection of the retina. However, no definitive evidence as yet exists regarding the actual cause of the vascular retinopathy seen in AIDS patients.

Key words: acquired immunodeficiency syndrome (AIDS), cotton-wool spots, cytomegalovirus retinitis, retinal vasculopathy, human immunodeficiency virus (HIV)

References


