



# Ophthalmic findings in patients with acquired immunodeficiency syndrome

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Ocular manifestations have been reported in up to 60% of individuals infected with human immunodeficiency virus (HIV) in the United States, and it is becoming increasingly apparent that these ocular manifestations almost invariably reflect extent of progression of the disease. The prevalence of ocular abnormalities among acquired immunodeficiency syndrome (AIDS) patients in Taiwan has not been reported. In the present study, we examined and followed up the ophthalmic conditions of a total of 274 HIV-infected patients during the period from March 1993 to May 1999. The results show that cotton-wool spots was the most common ocular finding in this series of patients with AIDS, occurring in 22 (32.8%) of 67 AIDS patients. Cytomegalovirus (CMV) retinitis was the most commonly seen opportunistic ocular infection, occurring in 14 (20.8%) of 67 AIDS patients. These findings suggest that AIDS patients should be closely followed for signs of opportunistic ocular disease which may initially be asymptomatic. Close co-operation between the ophthalmologist and the internist is essential to ensure timely therapeutic intervention, which can decrease the risk of further complications including visual impairment and blindness.

**Key words:** Acquired immunodeficiency syndrome (AIDS), cotton-wool spot, cytomegalovirus (CMV) retinitis

The epidemic of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) emerged in the last quarter of the 20th century, and within less than two decades has affected over 190 countries [1-4]. In Taiwan, the first case of AIDS was reported in December 1984. As of the end of 1998, a total of 2131 cases of anti-HIV positivity had been identified. AIDS is a potentially lethal severe multisystemic disease characterized by profound disruption of the immune system and a propensity for opportunistic infections and neoplasm. It is possible that some of the common ocular manifestations of AIDS are the result of infection by HIV [1,2]. Indeed, ocular involvement occurs in up to 70% of AIDS patients, with the most common lesions being a noninfectious retinal vasculopathy consisting of cotton-wool spots and retinal hemorrhage. Cytomegalovirus (CMV) retinitis has been reported in 15% to 40% of AIDS patients in the United

States, and in contrast to the noninfectious retinal vascular lesions of AIDS, demands aggressive treatment to prevent severe loss [4,5]. Although AIDS has drawn increasing public concern in Taiwan, the characteristics and prevalence of ocular abnormalities in Taiwanese patients with AIDS have not been reported. To determine the incidence and characteristics of the clinical ocular findings in AIDS patients in Taiwan, we performed complete ophthalmologic examinations and follow-up to 274 HIV-infected patients from March 1993 to May 1999. This report describes the epidemiologic characteristics of the ocular findings in these patients, the range of opportunistic infections acquired, and the ocular manifestations of AIDS in these patients.

## Patients and Methods

### Study participants and diagnostic criteria

The diagnosis of AIDS and HIV infection was based on the surveillance case definition adopted by the Centers for Disease Control [6]. The presence of HIV serum IgG was measured by enzyme linked immunosorbent assay (ELISA) (Murex Diagnostics,

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Dartford, UK). The serum IgG specificity to HIV-1 gene product was confirmed by Western blot (Sanofi Diagnostics Pasteur, Inc., Chaska, MN, USA).

### Ophthalmic examination and blood survey

All patients included in the study were referred by the Section of Infectious Diseases of Taipei Veterans General Hospital to the Department of Ophthalmology for ocular examination. Ocular examination included best-corrected visual acuity, binocular microscopy, and dilated fundus examination with indirect ophthalmoscopy. All patients had their fundi photographed, and patients underwent fluorescein angiography (5 mL of 10% sodium fluorescein intravenously).

CD4 cell counts were determined for each patient using a blood specimen obtained at the time of the first eye fundus examination. The CD4 cell counts were also determined in each case at diagnosis of CMV retinitis or other ocular abnormalities. Diagnoses of CMV retinitis and ocular abnormalities in each patient were made based on the clinical findings of indirect ophthalmoscopy, fluorescein angiography, and eye fundus photography. Once a diagnosis of CMV retinitis was established, intravenous ganciclovir treatment (F. Hoffmann-La Roche Ltd., Basel, Switzerland) was initiated using an induction dose of 5 mg/kg in every 12 h for 2 weeks, and then a maintenance dose of 5 mg/kg/day for 5 days per week in the following 2 weeks.

### Results

A total of 89 HIV-infected patients (67 AIDS patients and 22 HIV carriers) were included in the study group and underwent ophthalmologic examinations during the period from March 1994 to December 1997. In the 89 HIV-infected patients, there were 68 (76.4%) men and 21 (23.6%) women. The median age was 38 years, with a range from 18 to 74 years. Careful questioning of 89 HIV-infected patients revealed that 41 of the 89 (46.1%) were heterosexual, 37 (41.6%) were homosexual or bisexual, and seven (7.8%) had hemophilia. There were four (4.5%) patients who were both intravenous

drug abusers and were heterosexual. There were 87 Chinese, one Thai, and one African black. The median CD4 cell count of the 89 HIV-infected patients was 54 cells/ $\mu$ L (range 0-474 cells/ $\mu$ L). Opportunistic infections were diagnosed in 67 of these AIDS patients as shown in table 1. There were 47 patients with oral candidiasis and 36 patients with *Pneumocystis carinii* pneumonia as their major opportunistic infections. Other opportunistic infections identified included esophageal candidiasis in five patients, *Mycobacterium avium* in nine patients, herpes zoster in six patients,

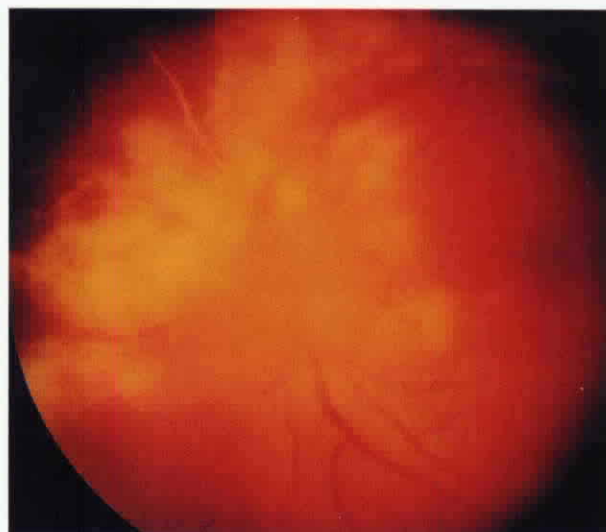


Fig. 1. Eye fundus photograph in an AIDS patient with CMV retinitis showing large retinal necrotic areas with retinal hemorrhage, exudate, and diffuse edema.

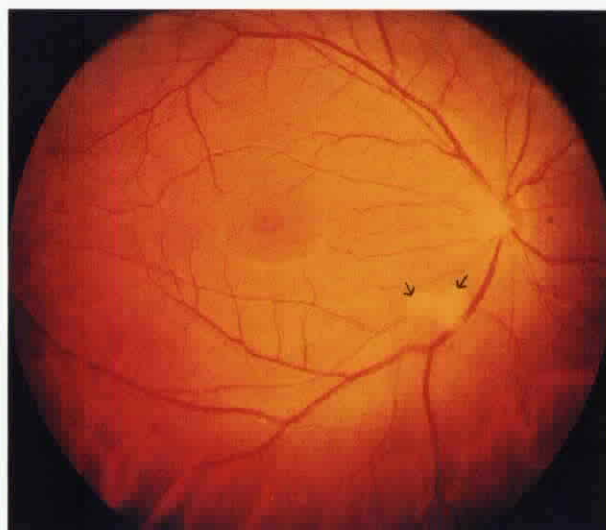


Fig. 2. Eye fundus photograph showing cotton-wool spots as appearing as fluffy white retinal opacities with indistinct borders.

Table 1. Opportunistic infections in the 67 AIDS patients

	No. of patients
Oral candidiasis	47
<i>Pneumocystis carinii</i> pneumonia	36
<i>Mycobacterium avium intracellulare</i>	9
Herpes zoster	6
Esophageal candidiasis	5
Kaposi's sarcoma	3
Lymphoma	2

Kaposi's sarcoma in three patients, and lymphoma in two patients.

During the same time period, the 67 patients with a diagnosis of AIDS underwent ophthalmologic examination. The mean age of these 67 patients was 42 years (range 22-74 years). There were 52 (77.6%) men and 15 (22.4%) women. The risk categories for these 67 AIDS patients included homosexual or bisexual men in 54%, heterosexual or sexual transmission in 39%, hemophilia in 6%, and intravenous drug abuse in 1%. At the time of the ophthalmic examination, CD4 cell counts were below 50 cells/ $\mu$ L (from 0-47 cells/ $\mu$ L, median 27 cells/ $\mu$ L) in 42 patients, and above 50 cells/ $\mu$ L (from 53-154 cells/ $\mu$ L, median 83 cells/ $\mu$ L) in 25 patients. The median CD4 cell count of the 67 AIDS patients was 36 cells/ $\mu$ L (range 0-154 cells/ $\mu$ L). CMV retinitis (Fig. 1) was clinically diagnosed in 14 of the 67 AIDS (20.8%) patients. At the time of CMV retinitis diagnosis, the median CD4 cell count among these patients was 7 cells/ $\mu$ L (range 0-27 cells/ $\mu$ L). After the 4-week ganciclovir treatment, 14 AIDS patients with clinical CMV retinitis showed improvement in retinal lesions with recovery and scarring in the affected areas. Based on ophthalmoscopic findings, HIV-related retinopathy (cotton-wool spots) (Fig. 2) was diagnosed in 22 of the 67 (32.8%) AIDS patients. The median CD4 cell counts in these patients was 26 cells/ $\mu$ L (range 0-87 cells/ $\mu$ L) at the time of first diagnosis.

The 22 patients with asymptomatic HIV infection included 16 (72.7%) men and six (27.3%) women. The mean age of these patients was 37 years (range 18-63 years). The risk factors for HIV in this group included homosexual or bisexual men in 43%, heterosexual or sexual transmission in 52%, and hemophilia in 6%. The median CD4 cell count in these 22 patients was 289 cells/ $\mu$ L (range 213-474 cells/ $\mu$ L). However, none of these patients had HIV-related retinopathy or other ocular infections.

## Discussion

Cotton-wool spots have been reported to be the most frequent ocular finding in AIDS patients [1-3]. In the present series, cotton-wool spots (Fig. 2) were found in 22 of the 67 (32.8%) AIDS patients. Because of the transient nature of these lesions, and the fact that several patients received only one ocular examination, the actual incidence of cotton-wool spots among AIDS patients in Taiwan may be higher than our results indicate [3,7]. Cotton-wool spots appear as fluffy white retinal opacities with indistinct borders [1-3,7] and result from stasis of axoplasmic flow in the nerve fiber layer of the retina. They may be ischemically induced

[2,7,8]. Cotton-wool spots are a nonspecific finding seen in a variety of diseases including diabetes, hypertension, anemia, and systemic lupus erythematosus [1,2,7]. None of the AIDS patients in our series had any of these diseases which are commonly associated with cotton-wool spots.

The occurrence of cotton-wool spots, retinal hemorrhages, and fluorescein angiographic changes in the AIDS patients of this series suggests the presence of retinal microvascular abnormalities [7,8]. To our knowledge, vascular changes have not been documented in other organ systems in patients with AIDS. The etiology of ocular vascular changes in AIDS patients is unclear [8]. Thus, in asymptomatic patients seen for routine ophthalmic evaluation, and especially in patients who belong to a high-risk group, the presence of cotton-wool spots without a discernible cause should alert the clinician to the increased likelihood of AIDS.

CMV retinitis is the most common ocular opportunistic infection in AIDS patients [1-5]. In the present series, CMV retinitis was found in 20.8% of AIDS patients during the 3-year study period. In general, patients have had AIDS for many months before developing CMV retinitis, which usually becomes manifest in the terminal stages of the disease [4,5,9-11]. CMV retinitis is characterized by a "crumbled cheese and ketchup" or "pizza pie" appearance, with large areas of retinal hemorrhage seen against a background of whitened, necrotic retina [4, 5]. CMV retinitis severely impairs the quality of remaining life in AIDS patients, especially in those with blood CD4 cell counts below 50 cells/ $\mu$ L [9-11]. In the present series, the mean CD4 count among AIDS patients with CMV retinitis was 7 cells/ $\mu$ L.

Although initial symptoms and signs of CMV retinitis may be minimal and ignored, the destructive and invasive nature of CMV retinitis can result in blindness if left untreated [9,10,12,13]. CMV retinitis in AIDS patients often present as a silent peripheral retinal lesion at the early stage, instead of an apparent lesion with prominent symptoms of decreased acuity [4,5,9,10]. It is important to note that the initial peripheral lesion may be missed if ophthalmologists do not use an indirect ophthalmoscope to view through a dilated pupil during the eye fundus examination [9, 10,12]. The classic appearance of fluffy, white exudate is often associated with large hemorrhage and the subsequent sheathing of the retinal vessels which lead to blindness [10-13]. Early detection and timely treatment are therefore crucial [14,15]. Because AIDS patients with CD4 lymphocytes count lower than 50 cells/ $\mu$ L have a higher risk of CMV retinitis, they should

be receive frequent ophthalmic follow-up. Internist and ophthalmologist should be alert to the possibility of asymptomatic CMV retinitis, and the need to ensure timely therapeutic intervention in order to decrease the risk of visual impairment and blindness.

The ophthalmologist has two major roles in treating AIDS patients. The first role is diagnosis. Ocular manifestation associated with AIDS should be strongly suspected in high-risk patients. The second major role of the ophthalmologist is to assist in the evaluation of new therapies for AIDS patients. The status of CMV retinitis provides a unique opportunity to monitor effectiveness in therapeutic trials. If regression of existing lesions and a halt in the development of new lesions is observed, it may suggest that a given therapy is effective.

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