

Ocular presentations in acquired immunodeficiency syndrome*

Pakitti Tayanithi**

Tayanithi P. Ocular presentations in acquired immunodeficiency syndrome. *Chula Med J* 1996 Sep;40(9): 745-53

The acquired immunodeficiency syndrome (AIDS) is a potentially lethal severe multisystemic disease characterized by profound disruption of the immune system and a propensity for various opportunistic infections and neoplasms. Ocular manifestations of AIDS may be seen in 75-100% of patients. A wide range of ocular pathologic changes occur in AIDS patients. Such conditions are generally classified into four major areas eg. noninfectious microangiopathy or AIDS retinopathy ; Opportunistic ocular infections, particularly cytomegalovirus (CMV) retinitis; conjunctival, eyelid or orbital involvement by those neoplasms seen in patients with AIDS (eg. Kaposi's sarcoma and lymphoma); neuro-ophthalmic lesions. Cytomegalovirus retinitis always was associated with a fatal outcome. Ophthalmologists should be aware of the syndrome and its ocular manifestations.

Key words : *AIDS, Acquired immunodeficiency syndrome, Cytomegalovirus retinitis, Cotton wool spot, Kaposi's sarcoma.*

Reprint request: Tayanithi P, Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. August 3, 1996.

* Presented at the "AIDS in 1996" workshop at The 15th Asia Pacific Congress of Ophthalmology (APAO), Hong Kong.

** Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University.

ปกิตติ ทยานธิ. อาการแสดงทางจักษุวิทยาที่พบในโรคภูมิคุ้มกันบกพร่อง. จุฬาลงกรณ์
เวชสาร 2539 ก.ย.;40(9): 745-53

โรคภูมิคุ้มกันบกพร่องหรือโรคเอดส์นั้นเป็นภาวะที่ทำให้เกิดโรคกับระบบการทำงานของร่างกายได้หลายระบบและมีความรุนแรงถึงชีวิต ลักษณะเฉพาะของโรคคือทำให้ภูมิคุ้มกันของร่างกายเกิดความบกพร่องอย่างรุนแรง เป็นผลทำให้เกิดการติดเชื้อแทรกซ้อนจากเชื้อโรคประเภทฉวยโอกาสหรืออาจเป็นมะเร็งบางชนิดได้ 75% ถึง 100% ของผู้ป่วยโรคภูมิคุ้มกันบกพร่องจะตรวจพบอาการทางจักษุวิทยาได้ อาการทางจักษุวิทยาที่พบได้ในผู้ป่วยโรคภูมิคุ้มกันบกพร่องอาจแบ่งเป็นกลุ่มใหญ่ ๆ ได้ 4 กลุ่ม ได้แก่ ความผิดปกติของเส้นเลือดฝอยที่ไม่ใช่สาเหตุจากการติดเชื้อ, การติดเชื้อประเภทฉวยโอกาสที่ตา โดยเฉพาะโรคจอประสาทตาอักเสบจากเชื้อไซโตเมกกะโลไวรัส, มะเร็งบางชนิด เช่น มะเร็งคาร์โปซิซาโคมา มะเร็งของต่อมน้ำเหลือง ซึ่งเกิดขึ้นที่เยื่อぶตา เปลือกตา หรือเบ้าตา, ความผิดปกติของระบบประสาทจักษุ โรคจอประสาทตาอักเสบจากเชื้อไซโตเมกกะโลไวรัสนี้มักจะพบในผู้ป่วยโรคเอดส์ระยะสุดท้ายที่มีอาการรุนแรงถึงเสียชีวิต จักษุแพทย์จึงควรทำความรู้จักกับโรคนี้และทราบถึงอาการแสดงทางจักษุวิทยาของโรคนี้ที่อาจจะตรวจพบได้

The acquired immunodeficiency syndrome (AIDS) is a severe eventually lethal multisystemic disease characterized by profound disruption of the immune system and a propensity for various opportunistic infections and neoplasms. It is manifested by the presence of opportunistic infections and characteristic neoplasms in persons infected with the human immunodeficiency virus (HIV), who have no other known cause of immunodeficiency.

HIV infection may damage or kill the CD4⁺ lymphocytes resulting in a reversal of the helper - to - suppressor T-cell ratio.⁽¹⁾ The CD4⁺ to CD8⁺ ratio is about 1.0 to 2.0 in healthy people. AIDS patients typically demonstrate ratios well under 1.0. The reversal of the normal helper-to-suppressor T-cell ratio results in a cell mediated immunoincompetence that is related to the occurrence of infection by selected opportunistic pathogens and the development of characteristic neoplasms.

HIV has been detected in the cornea,⁽²⁾ the conjunctival epithelium,⁽³⁾ and in tears,⁽⁴⁾ but at very low titers. It is noteworthy that lymphocytes and macrophages are the cells most susceptible to HIV infection.

The clinical spectrum of HIV infection and disease is variable and includes asymptomatic persons, persons with various constitutional signs and symptoms, and AIDS. It is currently believed that close to 100% of HIV seropositive patients will progress to AIDS. Immune system abnormalities may lead to opportunistic infections and malignant tumor formation in AIDS patients. Opportunistic infections are responsible for the deaths of most

AIDS patients. Cytomegalovirus (CMV) retinitis is often the initial sign of tissue-invasive systemic CMV infection in AIDS patients.⁽⁵⁾ Kaposi's sarcoma and non-Hodgkin's lymphoma are the two most common neoplasms seen in AIDS patients.

Ocular Presentations in AIDS

The initial report of the ocular manifestations of AIDS by Holland et al in 1982 focused on three major categories of ocular pathology, cotton wool spots, cytomegalovirus retinitis, and conjunctival Kaposi's sarcoma.⁽⁷⁾ More recent reports have confirmed these, and additionally noted cranial nerve paralysis, choroidal mycobacterium avium-intracellulare and toxoplasmic retinitis.⁽⁷⁻⁹⁾ It has become evident that ocular manifestations can be seen in the majority of the patients with AIDS.

The ocular manifestations of AIDS may be seen in 75-100% of patients. They are less common, but may still be seen, in patients with earlier, symptomatic HIV infection. Considering the high incidence of ocular lesions in AIDS patients and the improving ability to treat infections and neoplastic lesions, it is essential that ophthalmologists be thoroughly familiar with the ocular lesions seen in these patients.

A wide range of ocular pathologic changes occur in AIDS patients. Such conditions are generally classified into four major areas.

1. Noninfectious microangiopathy, most often seen in the retina, and sometimes called "AIDS Retinopathy".

2. Opportunistic ocular infections, particularly cytomegalovirus (CMV) retinitis.⁽¹⁰⁾
3. Conjunctival, eyelid or orbital involvement by those neoplasms seen in patients with AIDS (eg. Kaposi's sarcoma and lymphoma).⁽⁷⁾
4. Neuroophthalmic lesions⁽⁸⁾

The retinal microangiopathy is the most frequent ocular manifestation, and CMV retinitis is the most frequent opportunistic intraocular infection.

1. Noninfections retinal microangiopathy (AIDS retinopathy)

"AIDS retinopathy" is the most frequent form of ocular involvement in patients with AIDS (Table 1)

Table 1. Retinopathy in Patients with AIDS.

Condition	Occurrence(%)
AIDS retinopathy	66
Cotton wool spots	64
Intraretinal hemorrhage	12
Perivasculitis	<1
Retinal vascular occlusion	1

Multiple series^(6-8,10-13) have reported an abnormal eye examination in 52-100% of patients with AIDS. Cotton wool spots are the most common feature and have been reported in 28-92% of patients with AIDS, with most series reporting that over half of the patients have these lesions.

Cotton wool spots are microinfarctions of the nerve fiber layer of the retina. Ischemia disrupts

axonal transport, causing swelling of the axons in the nerve fiber layer and producing the characteristic white patches with feathered edges on the surface of the retina, and is sometimes associated with small hemorrhages. In AIDS, these lesions are usually confined to the posterior pole near the optic disc. Cotton-wool spots appear suddenly and disappear in approximately 2 months. Cotton-wool spots seem not to result in visual disturbances. Although the causes of focal retinal ischemia in those AIDS patients are unknown, possibilities include a direct toxic effect of HIV on vascular endothelium, deposition of circulating immune complex,⁽⁵⁾ disseminated intravascular coagulopathy, and rheologic problems from increased RBC aggregation and blood viscosity. It is possible that in the CNS these same effects may help explain encephalopathy associated with AIDS. There is no specific treatment for the cotton wool spots seen in HIV infection. There is some suggestion that the presence and number of cotton wool spots may reflect the patient's general condition and that they may predict the progression of AIDS.

Table 2. Retinopathy and HIV Infection.

Groups	Retinopathy (%)
AIDS	66
ARC	40
Asymptomatic HIV infected individuals	1
noninfected homosexual men	0

Retinal Hemorrhages

Retinal hemorrhages are seen in AIDS in association with CMV retinitis, cotton - wool spots, and in isolation. Retinal hemorrhages usually take the form of flame-shaped lesions in the posterior pole, dot and blot hemorrhages, or as punctate intraretinal hemorrhages peripherally. Occasionally, the hemorrhage will be manifest as Roth's spots (hemorrhage with white central area).⁽⁷⁾ Vision loss from retinal hemorrhage has not been described and treatment is conservative if the lesions are not associated with CMV retinitis or septicemia.

2. Opportunistic Ocular Infections

Multiple opportunistic agents have been documented to infect the eye in patients with AIDS (Table 3). The most common of these is CMV retinitis, but other opportunistic ocular infections include herpes zoster ophthalmicus, Pneumocystis choroiditis, varicella-zoster retinitis and toxoplasmic retinitis.

Table 3. Opportunistic Ocular Infections in Patients With AIDS.

Conditions	Occurrence (%)
Cytomegalovirus retinitis	20 - 25
Herpes zoster ophthalmicus	4
Toxoplasmic retinitis	1 - 2
Pneumocystis choroiditis	< 1
Fungal retinitis or endophthalmitis	< 1
Infectious keratitis	< 1

Cytomegalovirus (CMV) Retinitis

CMV retinitis is the most common intraocular infection in patients with AIDS.⁽¹³⁾ Approximately 20-25% of patients with AIDS will ultimately develop CMV retinitis at some time during the course of their disease. CMV retinitis severely impairs the quality of the remaining life in AIDS patients and, in contrast to the noninfectious lesions of AIDS, demands aggressive treatment to prevent severe visual loss.⁽²⁾ While it was initially suggested that CMV retinitis was a preterminal event,⁽⁷⁾ it is now recognized that CMV retinitis may occur at any time during the course of AIDS.⁽⁵⁾

CMV retinitis is associated with a profound immunodeficiency.⁽¹¹⁾ Survival after the diagnosis of CMV retinitis is approximately 6-8 months but appears to be increasing. Hepatitis may be present and blood cultures and urine specimens are usually positive for CMV. CMV infects the retina as well as the central nervous system (CNS), the reticuloendothelial system, kidneys, adrenals, lungs and gastrointestinal system. CMV retinitis is often the presenting sign of systemic CMV infection and all patients should have a thorough systemic evaluation performed.

CMV retinitis in the AIDS patient is usually the result of hematogenous seeding of CMV infected monocytes to the retina.

The diagnosis of CMV retinitis can usually be reliably made on ophthalmoscopy by an experienced observer. CMV retinitis may be asymptomatic, particularly if the lesion is small

or anterior, or minimally symptomatic. Often, the patient complains only of floaters or a vague sense of blurred vision. For more posteriorly located lesions, the patients often complain of a scotoma or a loss of vision.

The classic form of CMV retinitis is the hemorrhagic type, which has been termed **"Crumbled cheese and ketchup"** or **"pizza pie"**. Large areas of retinal hemorrhage are seen against a background of whitened, necrotic retina. With extensive hemorrhage, the appearance may simulate a central retinal vein occlusion or branch vein occlusion. Primary CMV involvement of the optic nerve results in a yellow-white disc with small hemorrhages. Often, the peripapillary retina is involved, resulting in a necrotizing neuroretinitis with markedly diminished vision. The diagnosis of CMV retinitis is a clinical one suggested by the presence of a white, necrotic, enlarging retinitis, with or without hemorrhage, in an immunocompromised patient. Equivocal lesions should be watched for progression without treatment. Positive blood and urine cultures for CMV are not diagnostic for CMV retinitis, because many AIDS patients have CMV viremia without retinitis. Vitreous cultures are usually negative in the presence of CMV retinitis. The differential diagnosis for CMV retinitis includes cotton-wool, spots, toxoplasmosis, Candida, syphilis, herpes simplex, and herpes zoster retinitis.

Toxoplasmic retinitis

Toxoplasma is a common cause of retinitis in the AIDS patients and is second only to CMV

retinitis.⁽¹⁵⁻¹⁷⁾ It occurs in 1-2% of patients with AIDS. Toxoplasmic retinitis in immunocompetent persons usually results from reactivation of latent, congenitally toxoplasmic cysts in the retina. In contrast, toxoplasmic retinitis in AIDS appears to occur during the course of newly acquired primary infection or from dissemination to the retina from latent extraocular sites.⁽¹⁸⁾

Patients may complain of floaters, photophobia, and decreased vision. Examination typically reveals a granulomatous anterior uveitis with moderate to severe vitritis, although vitritis may be minimal in some cases. Areas of necrotizing retinitis may be multifocal or bilateral.

Toxoplasmic retinitis does not resolve spontaneously in the AIDS patient, and treatment is required. Most lesions respond to treatment with pyrimethamine and sulfadiazine in standard doses. Long term maintenance therapy is generally required in order to prevent relapse of the disease.

Fungal retinitis

Candida retinitis and/or endophthalmitis has been reported in patients with AIDS, but occurs in less than 1% of such patients.

Syphilitic retinitis

Patients with AIDS have a relatively high incidence of coexisting sexually transmitted disease, including syphilis. The manifestations of syphilis in the AIDS patients are typically more severe, prolonged, difficult to treat and more likely to recur than in immunocompetent persons. Examination reveals a nongranulomatous fibrinoid anterior

uveitis, retinal phlebitis, and necrotizing retinitis.

The diagnosis of syphilis depends on a positive syphilis antibody test (VDRL, FTA-ABS). Treatment is that for neurosyphilis.

Other herpes virus infection

Clinically, infection of the retina with the varicellazoster virus appears to be identical to the acute retinal necrosis (ARN) syndrome, which is also caused by varicella-zoster, except that it occurs in patients who are HIV infected. The infection is a peripheral necrotizing retinitis. The retinitis has much less hemorrhage than fulminant CMV retinitis.

Herpes zoster ophthalmicus

Herpes zoster ophthalmicus occurs in approximately 4% of patients with AIDS and 3% of patients with ARC.⁽¹³⁾ Ocular complications, including scleritis, iridocyclitis, and sixth nerve palsies, occur in 80% of patients with herpes zoster ophthalmicus and HIV infection. Furthermore, in appropriate populations, herpes zoster ophthalmicus in young men appears to be a marker for HIV infection,^(2,19,20) even without other manifestations of HIV.

3. Ocular Neoplasms

Ocular involvement by Kaposi's sarcoma has been reported in 2% of patients with AIDS. Of patients with AIDS and Kaposi's sarcoma, 15-22% will develop ocular involvement.^(13,21) Either the eyelids or the conjunctiva may be involved. Conjunctival Kaposi's sarcoma usually

does not require treatment. Eyelid involvement by Kaposi's sarcoma may occasionally require therapy when the vision is compromised because of lid edema and /or tumor. If treatment is needed, radiation therapy appears to be most effective.⁽²¹⁾ Surgical resection is generally associated with recurrence.

In patients with HIV infection, high grade lymphoma is an AIDS defining disorder. Orbital involvement by lymphoma has been reported to occur in less than 1% of patient with AIDS.⁽¹³⁾

4. Neuroophthalmic Lesions

Neuroophthalmic lesions occur in approximately 8% of patients with AIDS.⁽¹³⁾ These lesions include cranial nerve palsies, papilledema, optic neuropathy, and hemianopsias.⁽¹³⁾ The most common etiology for neuroophthalmic lesion is cryptococcal meningitis,⁽¹³⁾ accounting for 60% of cases. Other causes include herpes zoster ophthalmicus, viral encephalitis, ethambutal toxicity, and CNS lymphoma.

Keratoconjunctivitis sicca occurs in 10-15% of AIDS patients.⁽¹⁰⁾ The etiology is unknown.

Subconjunctival hemorrhage may occur and is usually due to thrombocytopenia or is related to associated orbital disease. Subconjunctival hemorrhage should be differentiated from early Kaposi's sarcoma by careful serial observation to assess progression. Biopsy can provide definite diagnosis in suspected cases.

Noninfections peripheral corneal ulceration similar to that seen in patients with collagen

vascular disease has been reported, presumably on the basis of circulating immunoglobulins and immune complex.⁽²²⁾

Acute angle-closure glaucoma and acute glaucomatous attack has rarely been reported in patients with AIDS.⁽²³⁻²⁴⁾

References

1. Fauci AS. The human immunodeficiency virus: infectivity and mechanisms of pathogenesis, *Science* 1988 Feb 5; 239(4840): 617-22
2. Sandor EV, Millman A, Crosson TS, Mildvan D. Herpes zoster ophthalmicus in patients at risk for the acquired immune deficiency syndrome (AIDS). *Am J Ophthalmol* 1986 Feb 15; 101(2): 153-5
3. Fujikawa LS, Salahuddin SZ, Ablashi D, Palestine AG, Masur H, Nussenblast RB, Gallo RE. Human T-cell leukemia/lymphotropic virus type III in the conjunctival epithelium of a patient with AIDS. *Am J Ophthalmol* 1985 Oct 15; 100(4): 507-9
4. Fujikawa LS, Salahuddin SZ, Palestine AG, Masur H, Nussenblatt RB, Galls RC. Isolation of human T-cell leukemia/lymphotropic virus type III (HIV III) from the tears of a patient with acquired immunodeficiency syndrome (AIDS). *Lancet* 1985 Sep 7; 2(8454): 529-30
5. Henderly DE, Freeman WR, Smith RE, Causey D, Rao NA. Cytomegalo-virus retinitis as the initial manifestation of the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1987 Mar 15; 103(3pt1): 316-20
6. Holland GN, Gottlieb MS, Yee RD, Schanker HM, Pettit TH. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. *Am J Ophthalmol* 1982 Apr; 93(4): 393-402
7. Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immunodeficiency syndrome: ocular manifestations. *Ophthalmology* 1983 Aug; 90(8): 859-73
8. Rosenberg PR, Uliss AE, Friedland GH, Harris CA, Small CB, Klein RS. Acquired immunodeficiency syndrome: Ophthalmic manifestations in ambulatory patients. *Ophthalmology* 1983 Aug; 90(8): 874-8
9. Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Discussion of paper by Holland. Acquired immunodeficiency syndrome: ocular manifestations. *Ophthalmology* 1983 Aug; 90(8): 872-3
10. Khadem M, Kalish SB, Goldsmith J, Fetkenhour C, O'Grady RB, Phair JP, Chrobak M. Ophthalmologic findings in acquired immune deficiency syndrome (AIDS). *Arch Ophthalmol* 1984 Feb; 102 (2): 201-6
11. Palestine AG, Rodrigues MM, Macher AM, Chan CC, Lane HC, Fanci AS, Masur H, Longo D, Reichert CM, Steir R. Ophthalmic involvements in acquired immunodeficiency syndrome. *Ophthalmology* 1984

- Sep; 91(9): 1092-9
12. Schuman JS, Orellana J, Friedman AH, Teich SA. Acquired immunodeficiency syndrome (AIDS). *Surv Ophthalmol* 1987 May-Jun; 31(6): 384-410
 13. Jabs DA, Green WR, Fox R, Polk BF, Bartlett JG. Ocular manifestations of acquired immunodeficiency syndrome. *Ophthalmology* 1989 Jul; 96(7): 1092-9
 14. Jabs DA, Enger C, Bartlett JG. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. *Arch Ophthalmol* 1989 Jan; 107(1): 75-80
 15. Weiss A, Margo CE, Ledford DK, Lockey RF, Brinser JH. Toxoplasmic retinochoroiditis as an initial manifestation of the acquired immune deficiency syndrome. *Am J Ophthalmol* 1986 Feb 15; 106(2): 248-9
 16. Holland GN, Engstrom RE Jr, Berger BB, Daniels SA, Sidikaro Y, Harmon JA, Fischer DH, Boyer DS, Rao NA, Glasgow GT. Ocular toxoplasmosis in patients with the acquired immune deficiency syndrome. *Am J Ophthalmol* 1988 Dec 15; 106(6): 653-67
 17. Smith RE. Toxoplasmic retinochoroiditis as an emerging problem in AIDS patients. *AM J Ophthalmol* 1988 Dec 15; 106(6): 738-9
 18. Parke DW 2d, Font RL. Diffuse toxoplasmic retinochoroiditis in a patient with AIDS. *Arch Ophthalmol* 1986 Apr; 104(4): 571-5
 19. Cole EL, Meisler DM, Calabrese LH, Holland GN, Mondino BJ, Conant MA. Herpes zoster ophthalmicus and acquired immune deficiency syndrome. *Arch Ophthalmol* 1984 Jul; 102(7): 1027-9
 20. Kestelyn P, Stevens AM, Bakkers E, Rounroy D, Van de Perre P. Severe herpes zoster ophthalmicus in young Africa adults: a marker for HTLV-III seropositivity. *Br J Ophthalmol* 1987 Nov; 71(11): 806-9
 21. Shuler JD, Holland GN, Miles SA, Miller BJ, Grossman I. Kaposi's the conjunctiva and eyelids associated with the acquired immunodeficiency syndrome. *Arch Ophthalmol* 1989 Jun; 107(6): 858-62
 22. Pflugfelder SC, Saulson R, Ullman S. Peripheral corneal ulceration in a patient with AIDS-related complex. *Am J Ophthalmol* 1987; 104: 542
 23. Ullman S, Wilson RP, Schwartz L. Bilateral angle-closure glaucoma in association with the acquired immune deficiency syndrome. *Am J Ophthalmol* 1986 Apr 15; 101(4): 419-24
 24. Ubolsing S, Tayanithi P. Panophthalmitis in the acquired immune deficiency syndrome (AIDS) patient presenting as an Acute glaucoma, a case report. *Chula Med J.* 1990 Feb; 35(2): 99-103