Symposium

Posterior segment manifestations of human immunodeficiency virus/ acquired immune deficiency syndrome

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Ocular manifestations can occur in up to 50% of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients and posterior segment involvement is the most common presentation. The posterior segment manifestations of AIDS can be divided into four categories: retinal vasculopathy, opportunistic infections, unusual malignancies and neuro-ophthalmologic abnormalities. Retinal microvasculopathy and cytomegalovirus (CMV) retinitis are the most common manifestations, even in the era of highly active anti-retroviral therapy (HAART). Highly active anti-retroviral therapy has been shown to cause regression of CMV retinitis, reduce the incidence of CMV-related retinal detachments, and prolong patient survival. Immune recovery uveitis is a new cause of vision loss in patients on HAART. Diagnosis and treatment are guided by the particular conditions and immune status of the patient.

Key words: Acquired immune deficiency syndrome, cytomegalovirus retinitis, highly active antiretroviral therapy, immune recovery uveitis, microvasculopathy, posterior segment

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As per the United Nations acquired immune deficiency syndrome (UNAIDS)/World Health organization (WHO) acquired immune deficiency syndrome (AIDS) epidemic update, December 2006, there are about 39.5 million (34.1-47.1 million) people globally living with human immunodeficiency virus (HIV).[1] Out of these, about 5.2-5.7 million people are from India.[2] In spite of the widespread use of highly active antiretroviral therapy (HAART) today, ocular manifestations of AIDS at some point affect 50 to 75% of infected persons, of which posterior segment involvement is the most common.[3] Also, the spectrum of ocular manifestations of AIDS in the developing world differs from that of developed nations.[4] The purpose of this article is to review all posterior segment manifestations of AIDS. The posterior segment manifestations in AIDS patients can be divided into four main categories: vasculopathy, opportunistic infections, unusual malignancies and neuro-ophthalmologic abnormalities.

Vasculopathy

Microvasculopathy is the most common ocular manifestation of AIDS, seen in about 40% to 60% of HIV-positive patients.[5] Clinically, it manifests as cotton-wool spots located in the posterior pole and may simulate small patches of cytomegalovirus (CMV) retinitis [Figure 1]. However, unlike CMV retinitis, cotton-wool spots are not associated with large amounts of hemorrhages, subtle iritis, or mild posterior vitritis. They have more rounded borders, and are usually oriented along the vascular arcades, and represent focal areas of ischemia in the nerve fiber layer. Most patients with retinal microvasculopathy are asymptomatic. Treatment is not indicated in most cases. The prevalence of microvasculopathy is inversely proportional to CD4+ count.

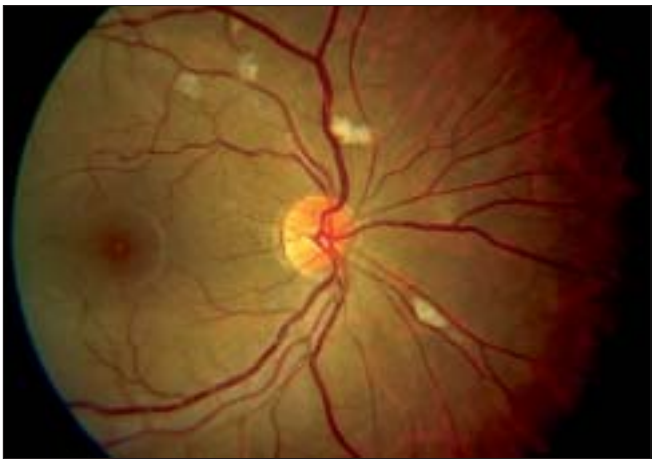

Figure 1: Microvasculopathy

Large vessel disease

Large vessel occlusions, including central and branch retinal vein occlusions and branch retinal artery occlusions are uncommon and usually occur in association with viral retinitis, infiltrative lymphomatous optic neuropathy, and as isolated abnormalities.[6-8] Frosted branch vasculitis has been associated with CMV retinitis in AIDS.[9]

Posterior segment opportunistic infections

Ocular posterior segment opportunistic infections are manifestations of disseminated disease in AIDS patients and are recognized either as necrotizing retinitis or as unifocal or multifocal choroiditis. Retinitis is more common than choroiditis. Retinitis in quiet eyes occurs in patients with lower CD4+ counts and is more commonly due to CMV and

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progressive outer retinal necrosis (PORN), while retinitis in inflamed eyes usually occur in patients with higher CD4+ counts and is more commonly due to acute retinal necrosis (ARN), toxoplasmosis, syphilis, or late stages of cryptococcus.

Cytomegalovirus retinitis

Cytomegalovirus retinitis is the most common AIDS-related ocular opportunistic infection and can develop in up to 40 to 50% of AIDS patients prior to HAART.[5] Although its incidence has declined markedly since the advent of HAART in the western world, it still remains the leading cause of ocular morbidity in the developing countries.[10] In India, CMV retinitis still remains the commonest ocular manifestation in AIDS cases.[11,12] In our series of 1286 cases, the incidence of CMV retinitis remains high even in the era of HAART [Table 1]. It may be unilateral to start with, but up to 52% will eventually develop bilateral disease. Cytomegalovirus retinitis occurs almost exclusively in patients whose CD4+ counts are <50 cells/μl.[13] However, its diagnosis cannot be excluded based on CD4+ count alone in patients taking HAART. In exceptionally rare instances, CMV retinitis may develop in patients with elevated CD4+ counts shortly after the initiation of HAART.

Table 1: Ocular manifestations in 1286 acquired immunodeficiency syndrome cases

Ocular lesions	Not on HAART (%)	On HAART (%)
Cytomegalovirus retinitis	39	24
Cotton-wool spots	22	16
Herpes zoster ophthalmicus	7	6
Retinal detachment	7	11
Ocular tuberculosis	0.5	5
Optic atrophy	2.8	4
Anterior Uveitis	2.1	3.8
Molluscum contagiosum	2.1	2.1
Blepharitis	1.8	1.4
Nerve Palsy	1.4	2.1
Papillitis	1.3	1.9
Acute retinal necrosis	1.1	1.2
Syphilis	1.1	1.4
Progressive outer retinal necrosis	1.1	0.8

HAART- highly active anti-retroviral therapy

Clinical findings: There are three clinical forms of CMV retinitis. The classical form (pizza pie retinopathy or cottage cheese with ketchup) is characterized by confluent retinal necrosis with hemorrhage that develops mostly in the posterior retina [Figure 2A]. The advancing edge of these lesions is usually very sharp and spreads contiguously. Typically, over several weeks untreated lesions progress to full-thickness necrosis with resultant retinal gliosis and pigment epithelial atrophy. Patients often have loss of visual field or visual acuity and scotoma. In contrast, the indolent form is recognized as a granular lesion in the peripheral retina, often with little or no hemorrhage [Figure 2B]. Patients may notice floaters, or they may be asymptomatic. A third uncommon presentation is frosted branch angiitis [Figure 2C]. Because approximately 15% of patients with active CMV retinitis are asymptomatic, routine screening with dilated indirect ophthalmoscopy has been recommended at three-month intervals in patients with CD4+ counts less than 50 cells/μl.[14] Cytomegalovirus retinitis may result in either serous or rhegmatogenous retinal detachment, although the latter is much more common. Rhegmatogenous retinal detachment has been reported in 13 to 29% of patients with CMV retinitis and may occur during the active or healed phase of the disease. However, since the advent of HAART, incidence of retinal detachment has decreased by approximately 60 to 77% in the western world.[15] In contrast, in our series, the incidence of CMV-related retinal detachment was found to have increased [Table 1]. This may be due to higher number of patients taking inappropriate HAART, or people taking HAART have larger areas of healed CMV retinitis which eventually develop necrotic holes leading to detachment. Various approaches including pars plana vitrectomy (PPV) with gas or silicone oil tamponade (preferably high viscosity 5000CS), scleral buckling and laser demarcation have been effective in the repair of retinal detachments related to CMV retinitis.[16]

Treatment: Treatment of CMV retinitis is individualized and depends upon the location of the active retinitis and the immune status of the patient. Currently available anti-CMV agents include ganciclovir and its prodrug valganciclovir, foscarnet, cidofovir, fomivirsen, ganciclovir implant and oral valganciclovir. A brief summary of these drugs is provided in Table 2.

Necrotizing herpetic retinopathy

Necrotizing herpetic retinopathy (NHR) is a continuous spectrum of posterior segment inflammation induced by herpes viruses, most commonly varicella zoster virus (VZV).

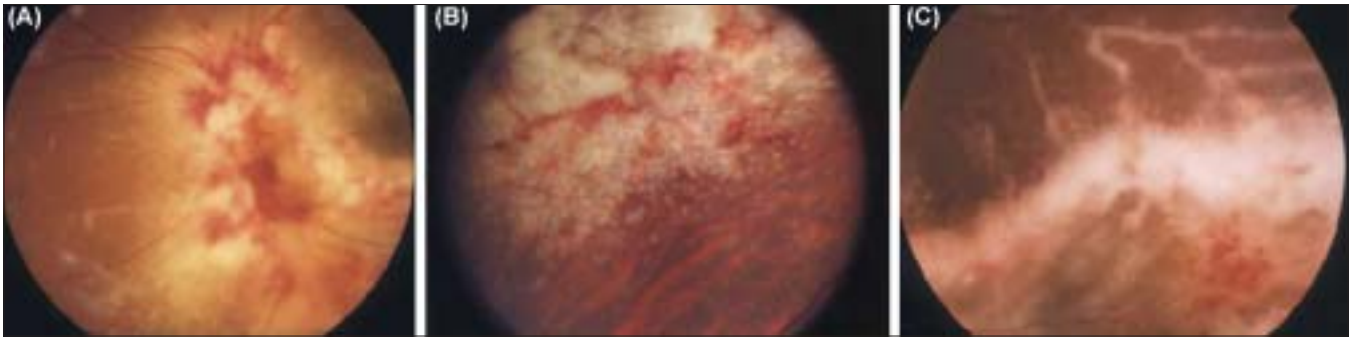

Figure 2: (A) Classic CMV retinitis: pizza-pie appearance. (B) Granular variety of CMV retinitis. (C) Frosted-branch angiitis variety of CMV retinitis

Table 2: Medications for cytomegalovirus retinitis

Medication	Route	Induction dose	Maintenance dose	Adverse effects
Ganciclovir	Intravenous	5 mg/kg bid for 2-3 weeks	5-10 mg/kg/day indefinitely	Neutropenia, anemia, thrombocytopenia, altered liver functions
	Oral	Not used	1 g tid indefinitely	Same as above
	Intravitreal	400-2000 µg twice/ week	400-2000 µg once/ week	Vitreous hemorrhage, retinal detachment
	Intraocular sustained-release Implant	6 mg pellet inserted surgically through pars-plana region	Replaced every 6-8 months	Vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, extraocular CMV
Foscarnet	Intravenous	90 mg/kg bid for 2-3 weeks	90-120 mg/kg/d indefinitely	Elevated creatinine, decreased Ca, Mg, K; tetany, perioral numbness, finger parasthesias
	Intravitreal	2400 µg twice/week	2400 µg once/week	Vitreous hemorrhage, retinal detachment
Cidofovir	Intravenous	5 mg/kg weekly for 2 weeks	5 mg/kg every other week	Proteinuria, renal failure, Fanconi's syndrome, neutropenia, uveitis
	Intravitreal	15 µg/0.1 ml	15 µg/0.1 ml every 6 weekly	Uveitis, ocular hypotony, IRU, vitreous hemorrhage, retinal detachment
Valganciclovir	Oral	900 mg bid for 3 weeks	900 mg/d	Neutropenia, anemia, thrombocytopenia, gastric disturbances
Fomivirsen	Intravitreal	330 µg on days 1 and 15	330 µg monthly	Vitreous hemorrhage, retinal detachment

bid - twice daily, tid - thrice daily, d - daily, IRU - immune recovery uveitis

Its two most recognizable clinical patterns are ARN [Figure 3] and PORN [Figure 4]. Usually, the former occurs in healthy persons and AIDS patients with only mild immune dysfunction and elevated CD4+ counts, whereas the latter usually develops in those who are severely immunosuppressed.[17] In addition to varicella zoster virus, herpes simplex virus and CMV have been isolated in patients with ARN, and herpes simplex in eyes with PORN.[18] The differential features between ARN, PORN and CMV retinitis are given in Table 3.

Aggressive medical treatment with appropriate systemic antivirals may improve long-term visual outcome in patients with NHR. Treatment of ARN includes intravenous acyclovir (1500 mg/sq, meter/day in three divided doses) for seven to 10 days followed by oral acyclovir (800 mg five times daily) for six weeks.[12] Following resolution of retinitis, prophylactic laser barrage is considered beneficial to prevent retinal detachment. However, visual loss due to progressive infection, optic nerve sheath effusion, or, in most cases, retinal detachment occurs in up to 70 to 85% of patients. Retinal detachment requires vitrectomy, intravitreal silicone oil tamponade and endolaser photocoagulation.

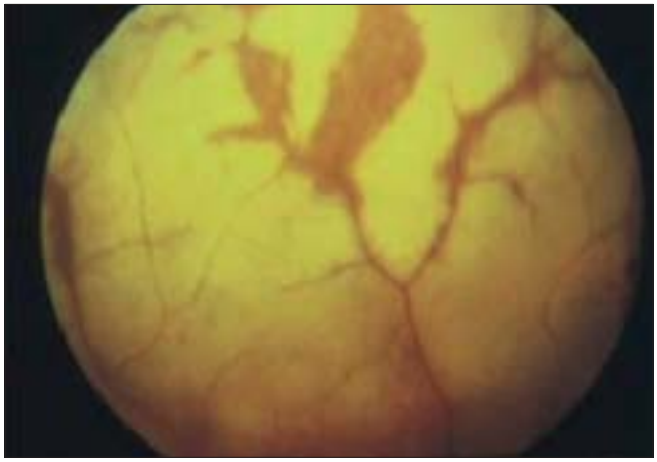

Figure 3: Acute retinal necrosis

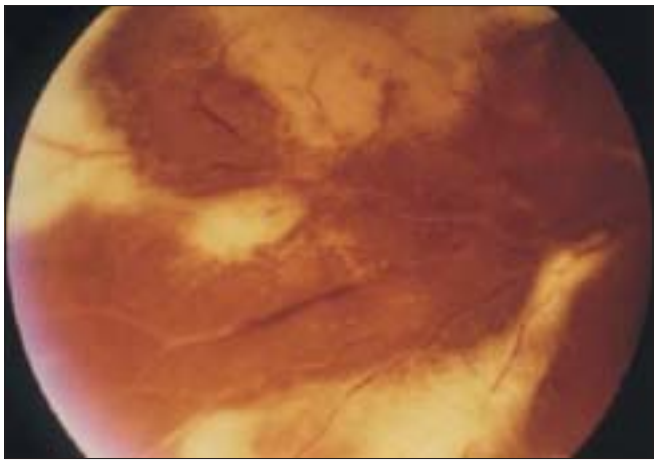

Figure 4: Progressive outer retinal necrosis

Toxoplasmosis

In the majority of AIDS cases, toxoplasmosis is a primary infection rather than a reactivation. Ocular toxoplasmosis in AIDS, in contrast to toxoplasmosis in immunocompetent individuals, is often bilateral, multifocal, and not associated with chorioretinal scars. It may cause a variety of ocular abnormalities including iritis, vitritis, choroiditis, multifocal or diffuse necrotizing retinitis [Figure 5], papillitis or retrobulbar neuritis, or outer retinal toxoplasmosis.[19] Toxoplasma retinitis may resemble CMV retinitis; however, intraocular inflammation is usually more severe and hemorrhages are fewer. Treatment with standard antiparasitic drugs

Table 3: Differentiating features of three types of viral retinitis in acquired immunodeficiency syndrome

	Acute retinal necrosis	Progressive outer retinal necrosis	Cytomegalovirus retinitis
Immune status	Healthy	Immunosuppressed	Immunosuppressed
Laterality	Bilateral 30-80%	Bilateral 71%	Bilateral 30-50%
Visual loss	Severe	Early loss of vision	Only if it involves macula
Anterior uveitis	Mild to moderate	Mild	Mild
Vitreous reaction	Significant vitritis	Minimal/no vitritis	Minimum/no vitritis
Retinal involvement	Full thickness	Deep outer retinal involvement	Full thickness involvement with granular border
Classic appearance	Late Swiss-cheese	Cracked mud	Pizza-pie
Vasculitis	Common	Uncommon	Seen but not common
Retinal hemorrhages	Common	Uncommon	Common in active lesion
Retinal detachment	Common	Common	Less common
Progression	Rapid	Rapid	Slow

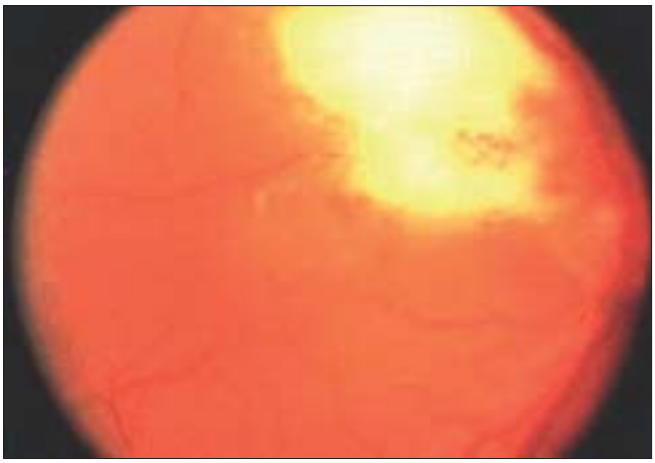

Figure 5: Toxoplasmic retinochoroiditis

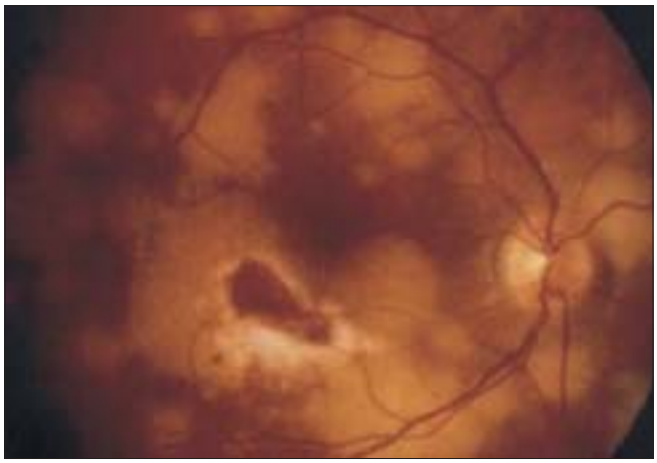

Figure 6: Pneumocystic choroiditis

(pyrimethamine, clindamycin, sulfonamides) is successful in controlling ocular toxoplasmosis in most cases.

Choroiditis

Pneumocystis

Ocular manifestations of *P. carinii* include conjunctivitis, orbital mass, optic neuropathy, and choroiditis.[20] It is seen as classically bilateral and multifocal yellowish, well-demarcated, choroidal lesions located in the posterior pole not associated with vitritis, iritis, or vasculitis [Figure 6].[21] Ocular lesions respond in most cases to induction and subsequent maintenance treatment with systemic pentamidine, trimethoprim and sulfamethoxazole, or dapsone.

Cryptococcus

Cryptococcus meningitis is the most common cause of AIDS-related neuro-ophthalmolgic lesions. Cryptococcal choroiditis may be multifocal, solitary, or confluent and may be associated with eyelid nodule, conjunctival mass, granulomatous iritis, iris mass, vitritis, necrotizing retinitis, endophthalmitis, and optic neuritis [Figure 7].[22] Fluconazole maintenance therapy 200 mg/day is currently recommended in all patients even in the era of HAART.

Ocular tuberculosis

Though pulmonary tuberculosis is the commonest systemic opportunistic infection seen in AIDS cases in India, the incidence of ocular tuberculosis is very low. In our study of 1286 cases, we found only 1% cases with presumed ocular tuberculosis. It usually presents as multifocal choroidal tubercles with discrete yellow lesions mainly at the posterior pole [Figure 8]. It may be associated with an exudative retinal detachment with variable vitreous inflammation. Occasionally, however, it may present as a big solitary posterior pole granuloma-like mass lesion [Figure 9].[23] Treatment with long-term systemic anti-tuberculous drugs is effective in most cases. The spectrum of ocular tuberculosis, however, is changing in today's era of HAART. Recently, there has been a report of worsening of ocular tuberculosis in HIV patients after antiretroviral therapy.[24]

Unusual malignancies

Reported posterior segment manifestations of non-Hodgkin's lymphoma (NHL) include necrotizing retinitis, multifocal choroiditis, retinal vasculitis, vitritis, subretinal mass, and pseudo-hypopyon uveitis.[25] Treatment options include radiation and chemotherapy.

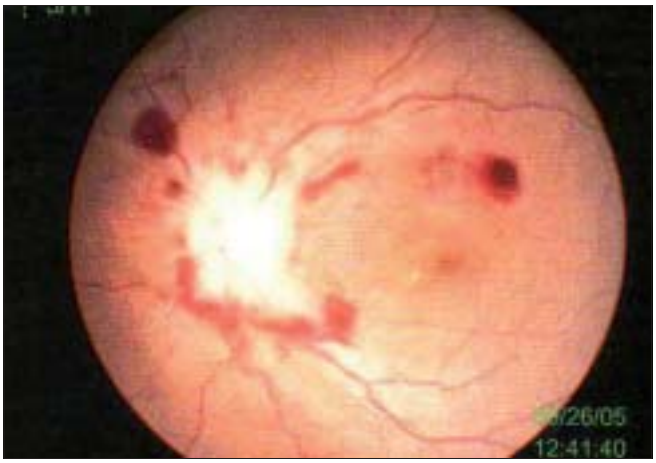

Figure 7: Cryptococcus involvement of optic nerve and retina

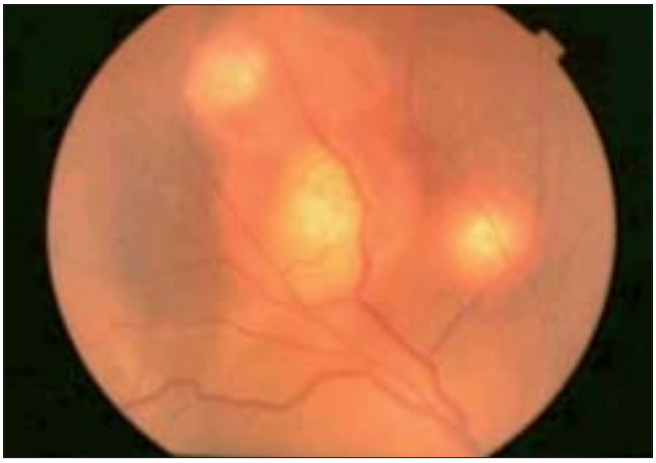

Figure 8: Multiple choroidal tubercles due to ocular tuberculosis

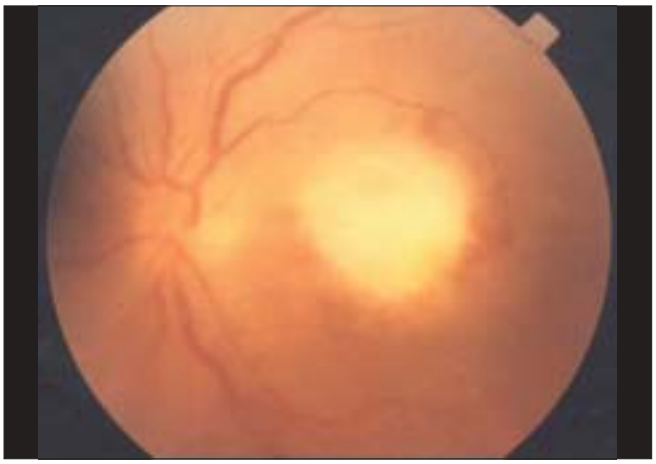

Figure 9: Solitary mass lesion due to ocular tuberculosis

Neuro-ophthalmologic abnormalities

Neuro-ophthalmologic abnormalities usually are an indication of infection or lymphoma of the brain or meninges and occur in only 6% of AIDS patients. Clinical abnormalities of the optic nerve in a patient with AIDS may be recognized as perineuritis, papilledema, papillitis, retrobulbar neuritis, and optic atrophy.[26]

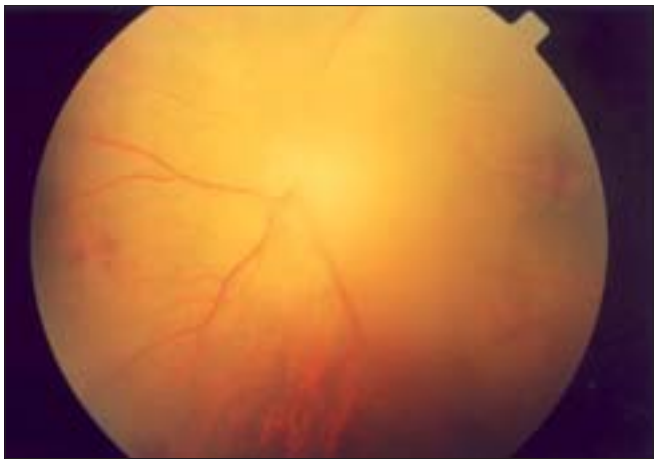

Figure 10: Severe vitritis due to immune recovery uveitis

Syphilis

Ocular syphilis in AIDS may present as iritis, vitritis, retrobulbar optic neuritis, perineuritis, papillitis, neuroretinitis, retinal vasculitis, a necrotizing retinitis which may be clinically indistinguishable from CMV and exudative retinal detachment.[27] Syphilis in AIDS may develop when CD4+ counts are greater than 200 cells/μl and, consequently, syphilis, including ocular syphilis, may be the presenting illness leading to the diagnosis of AIDS. It has been recommended that 12 to 24 million units of intravenous aqueous penicillin be administered for 10 days in AIDS patients with ocular syphilis.

Ocular manifestations of HIV in the era of HAART

The advent of potent antiretroviral therapy has had a profound impact on the ophthalmological manifestations of AIDS patients. As these drugs lead to improved immune function, patients have fewer opportunistic infections. There have been reports of dramatic decreases in the frequency of CMV retinitis in areas where three- and four-drug antiretroviral combination therapies are routinely being used. In addition to decreased incidence, there are improved outcomes in patients with CMV retinitis who received new active antiretroviral therapy in addition to anti-CMV therapy.[28] In many patients with healed CMV retinitis who have responded to HAART, anti-CMV therapy has been discontinued without reactivation of the retinitis. In our study where combination antiretroviral treatment was given to 12 patients with active CMV retinitis, all anti-CMV medications were omitted once the CD4 cell counts were >100/mm^3 for three months.[29] The median CD4 cell count increased from 36.5/mm^3 (range, 3 to 74/mm^3) at baseline to 175.5/mm^3 (range, 97 to 410/mm^3) at three months. No patient had reactivation of CMV retinitis or development of extraocular CMV during median follow-up of 16.7 months. Although at present there are no standardized criteria for determining whether immunologic improvement is sufficient to allow withdrawal of therapy, a CD4+ cell count of at least 100 cells/mcL for at least three to six months, or a rise of at

least 50 cells/mcL has been recommended.[30,31] Reactivation of CMV retinitis has been reported in patients who discontinue or become intolerant to HAART. When maintenance therapy is discontinued, close observation is required.

Immune recovery uveitis

Immune recovery uveitis (IRU) is a noninfectious intraocular inflammation which develops in patients with inactive CMV retinitis who have had a substantial elevation in CD4+ count with HAART. Immune recovery uveitis is the leading cause of new visual loss in persons with AIDS seen in about 16 to 63% of HAART responders. The severity of the inflammation depends on the degree of immune reconstitution, extent of CMV retinitis, amount of intraocular CMV antigen, and previous treatment. Clinical findings include anterior chamber or vitreous reaction [Figure 10], panuveitis with hypopon, optic disk and cystoid macular edema, epiretinal membrane formation, cataract, vitreomacular traction syndrome, and proliferative vitreoretinopathy.[32,33] Treatment with corticosteroids (subtenon or systemic or intravitreal) is effective in controlling inflammation and improving vision in some cases. However, surgery may be required in patients with vitreomacular traction syndrome, epiretinal membrane formation, cataract, and proliferative vitreoretinopathy.

Summary

CMV retinitis is much less common in the era of HAART but remains one of the commonest ocular complications of AIDS in India. Highly active anti-retroviral therapy has been shown to cause regression of opportunistic infections, including CMV retinitis, increase time to relapse of CMV retinitis, reduce the incidence of CMV-related retinal detachments, and prolong patient survival. Patients with inactive CMV retinitis who have responded to HAART with a CD4+ cell count >100 cells/mcL for more than three to six months may be candidates for discontinuation of CMV maintenance therapy. Close follow-up for any signs of reactivation is mandatory. Immune recovery uveitis has been reported in patients with healed CMV retinitis who have responded to HAART. Necrotizing herpetic retinopathy and ocular tuberculosis are other common posterior segment disorders seen in AIDS cases.

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