Changing Pattern of Ophthalmic Manifestation in AIDS Patients in Post HAART Era

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Abstract
Ophthalmic manifestations of AIDS comprise anterior segment as well as posterior segment. Anterior segment manifestations include bacterial, viral, fungal and protozoal infections, malignancies such as Kaposi sarcoma and squamous cell carcinoma and higher risk of cataract. Most common opportunistic infection is Cytomegalovirus (CMV) retinitis. Vasculopathy and neuro-ophthalmic complications are also a part of posterior segment manifestations. Since the advent of highly active antiretroviral therapy (HAART), incidence and severity of malignancies, opportunistic infections and CMV retinitis are decreasing. But the immune reconstitution due to HAART has led to emergence of immune recovery mediated inflammatory phenomenon which are potentially sight threatening.

Keyword: AIDS, CMV, HAART, Retinitis

Introduction:
Human Immunodeficiency Virus (HIV) was discovered in 1984¹, three years after the first case of Acquired Immunodeficiency Syndrome (AIDS) was identified.² Since then, a number of AIDS cases have risen globally leading to a pandemic affecting more than 35 million people across the world.³ Moreover, it affects the productive age group leading to a great socio-economic burden. In India about 2.4 million people are living with HIV of which 83% are from age group 15-49 years.⁴

Ophthalmic manifestations in AIDS patients used to involve 50%–75% of AIDS patients in pre highly active antiretroviral therapy (HAART) era⁵ and comprises both anterior segment and posterior segment.

HAART leads to improvement of immune status of the patient recognized by improvement in the CD4 cell count. Since the introduction of HAART, patient’s morbidity has been reduced and their survival has been prolonged. Also it has led not only to a change in the spectrum of ocular complications but also to emergence of newer ophthalmic manifestations. This is an attempt to review all the ophthalmic manifestation of AIDS and present an update of the new trend in ophthalmic manifestation in post HAART era.

Anterior Segment Complications due to HIV
Herpes Zoster Ophthalmicus (HZO)
HZO is caused by varicella zoster virus when it involves the trigeminal nerve. It remains latent in sensory ganglia in immunocompetent individuals but gets reactivated in local trauma or in immunocompromised states like old age, malignancy or HIV.

It leads to vesicobullous rashes over the trigeminal area with or without blepharitis, conjunctivitis, keratitis, secondary glaucoma, scleritis, retinitis, vasculitis, hypopyon or encephalitis.⁶ According to Hodge and associates, relative risk of HZO among HIV positive vs. HIV negative is 6.6:1.⁷ Martinez et al have observed increased incidence of Herpes Zoster
in AIDS patients after initiation of HAART. They noted that the increased incidence risk of herpes zoster was not dependent on age, sex, type of protease inhibitor or CD4+ cell counts but affected by increased CD8 cell counts.8

On the other hand Biswas et al reported that out of 120 patients on HAART, seven patients had HZO associated with increased CD4 cell count.9

Viral Keratitis
Ocular infection is usually caused by herpes simplex virus (HSV) but in AIDS patients ocular infection by HSV-2 has also been reported.10 AIDS patients as compared to non HIV infected patients have increased incidence of keratitis and more likely to have perforation.11 In AIDS patients corneal epithelial lesions have a tendency to be more marginal rather than central and more delicate and lacy rather than discrete or broad. They are also more chronic in nature, pleomorphic and with multiple components.12 Increased incidence of peripheral ulcerative keratitis has been reported in AIDS.13 The keratitis is more recurrent and more resistant to treatment.14 But the incidence of stromal involvement is lower as compared to their non-AIDS counterpart.13

CMV Keratitis
Although CMV infection is asymptomatic in immunocompetent individuals except transient conjunctivitis, it leads to epithelial and stromal keratitis,13 which may be associated with iritis,15 secondary glaucoma.16 CMV retinitis is the most common opportunistic infection in AIDS. Post HAART, CMV infection has been largely prevented by restoring the immunity in AIDS patients.

Molluscum Contagiosum
It is caused by pox virus and leads to nodular lesions on eyelids and conjunctiva which are larger, more confluent, more aggressive and resistant to treatment.17 Although administration of HAART leads to complete resolution and disappearance of the lesions, it does not prevent the recurrence albeit much less severe. Paradoxically, HAART by restoring the immunity, sometimes leads to newer presentation of molluscum like severe conjunctivitis.18

Bacterial Keratitis
Although spectrum of bacteria causing keratitis in AIDS is not very different from non AIDS patients, they are at increased risk from normal flora owing to preexisting dry eye and viral keratitis which allow secondary bacterial infection by causing epithelial erosions. Staphylococcus aureus, Staphylococcus and Pseudomonas. Klebsiella oxytoca, Streptococcus, Bacillus, Micrococcus, Neisseria & Capnocytophaga were known to cause keratitis19 and recently Acanthamoeba has been added to the list.20,21 In AIDS, keratitis is more severe, bilateral, involving multiple pathogens and has greater tendency to perforate.

Microsporoidal Keratitis
Microsporoidal keratitis is very uncommon in immunocompetent individuals22 whereas several cases have been reported in AIDS patients. It leads to epithelial keratitis associated with anterior chamber reaction and conjunctivitis.23,24 HAART administration leads to complete resolution of keratitis but some cases of immune recovery mediated reactivation of keratitis have occurred.25

Toxoplasmosis
In immunocompetent individuals toxoplasmosis causes anterior uveitis but secondary to necrotizing retinochoroiditis and is limited to neural retina. In AIDS, it causes primary toxoplasmosis, anterior uveitis even in the absence of retinal involvement.26

Tuberculosis
Mycobacterium causes ocular tuberculosis presenting as corneal ulcers, iris nodules, tubercles13, orbital and lacrimal granulomas, conjunctival masses and even panophthalmitis. In AIDS, it presents with intense reaction and hypopyon.27

Fungal infections
Fungal infections are caused by Candida, Cryptococcus Histoplasma and Pneumocystiscan which manifests as keratitis, conjunctivitis, limbal
infection, iris granulomas and scleral ulceration.\textsuperscript{28,29} While in immunocompetent individuals fungal infections are rare, in AIDS they occur spontaneously. In AIDS, fungal keratitis is more acute, bilateral, have more protracted course and higher risk of perforation.\textsuperscript{30}

**Treponema Pallidum**

Treponema causes chancres of the conjunctiva, gumma, uveitis and even panuveitis. In AIDS, it tends to be more aggressive, severe and relapsing.\textsuperscript{31,32}

**Adnexal lesions**

Preseptal cellulitis, most commonly due to Staphylococcus and lid abscesses due to Staphylococcus, AFB and CMV have been reported in AIDS patients.\textsuperscript{33}

**Neoplasms**

Kaposi sarcoma, the most common neoplasm in AIDS, involves the eyelids, conjunctiva and the orbit.\textsuperscript{34-37} The need of treatment modalities comprising radiation and chemotherapy has been reduced following HAART administration.\textsuperscript{38} Paradoxically, HAART sometimes leads to Immune Reconstitution Inflammatory Syndrome (IRIS) related complications, which can cause kaposi sarcoma.\textsuperscript{39,40} Non-Hodgkin's lymphoma (NHL), the second most common neoplasm in AIDS, affects eyelids conjunctiva and orbit presenting as rapidly enlarging erythematosus lesions,\textsuperscript{41} lid swelling, ptosis, proptosis, and ophthalmoplegia. In AIDS, NHL tends to be of a higher grade.\textsuperscript{42}

**Squamous Cell Carcinoma**

SCC, the third most common neoplasm in AIDS, presents as tumour of eyelid, conjunctiva and limbus.\textsuperscript{43} Invasive conjunctival SCC have been observed to completely regress after HAART.\textsuperscript{44} Bacillus angiomatosis which is vascular proliferation caused by Bartonella has been noted in AIDS patients and are at a higher risk of developing it once their CD4 cell count drops below 200 cell/mm\textsuperscript{3}.

**Miscellaneous**

KCS is more common in AIDS as compared to their immunocompetent counterparts.\textsuperscript{45} This could be due to HIV-mediated inflammatory destruction of lacrimal glands and also due to direct conjunctival damage caused by the virus itself. HAART has not been shown to reduce the incidence of KCS in AIDS patients.\textsuperscript{46} Non-specific culture negative conjunctivitis, trichomegaly,\textsuperscript{5} Atopic dermatitis,\textsuperscript{13} Blepharitis\textsuperscript{6} and Acute angle closure glaucoma\textsuperscript{46} have been observed in AIDS patients.

**Iatrogenic Features**

Due to induction of HAART in AIDS patients, the immunity gets improved. This has led to an entire new spectrum of ocular manifestation in the form of IRIS and more specifically Immune Recovery Uveitis (IRU) in up to 37% of AIDS patients on HAART.\textsuperscript{47} IRU involves the anterior uvea and vitreous and sometimes cause Cystoid macular oedema which can lead to marked disturbance of visual function.\textsuperscript{47-49} Also, drug induced anterior uveitis has been observed in those who are on medication like Rifabutin\textsuperscript{50} and Cidofovir.\textsuperscript{51} Stevens Johnson Syndrome\textsuperscript{13} has been noted in AIDS, which has been attributed to the multiple drugs they are subjected to in HAART and to the virus itself. Corneal phospholipidoses or vortex keratopathy has been observed due to toxic effects of antiviral drugs such as ganciclovir, acyclovir or atovaquone.\textsuperscript{52}

**Cataract**

AIDS patients with CMV Retinitis have been found to at an increased risk of cataract. This risk directly correlates with area of retina involved in CMV retinitis. The risk was not found instantaneous with the diagnosis but accumulative over a period of time.\textsuperscript{53}

**Posterior segment manifestations**

In AIDS, the posterior segment manifestations can classified into four categories: retinal vasculopathy, opportunistic infections, unusual malignancies and neuro-ophthalmologic complications.
Retinal Vasculopathy

The most common ophthalmic manifestation of AIDS is retinal microvasculopathy. It presents as cotton wool spots which have rounded borders, oriented along the vascular arcades, and represent areas of ischemia in the nerve fiber layer but are not associated with large amounts of hemorrhages, iritis, or vitritis. Large vessels involvement occurs in the form of central retinal vein occlusion, branch retinal vein occlusion, retinal arterial occlusions which may be associated with viral retinitis or optic neuropathy. The presence of HIV retinopathy is a sign of progression of HIV infection and an indication for the need to institute antiretroviral therapy.

Oppotunistic infections

Cytomegalovirus (CMV) Retinitis

Cytomegalovirus (CMV) Retinitis manifests in three different ways. The classical picture involves the posterior pole with cotton wool spots and hemorrhages which resembles pizza pie retinopathy or cottage cheese with ketchup appearance. The indolent form involves peripheral retina which presents as granular appearance with little hemorrhage. The third form presents as frosted branch angiitis. The complications are serous or rhegmatogenous retinal detachment. Before the advent of HAART CMV retinitis was the most common opportunistic infection. After the advent of HAART its incidence and progression has reduced in the western world but not in developing world. Similarly, the complication of retinal detachment has reduced in post HAART era in western world but failed to reduce in developing world.

Herpetic Retinopathy

Herpetic retinopathy is caused most commonly by varicella zoster virus (VZV). In immunocompetent individuals it presents as acute retinal necrosis (ARN) while in AIDS as progressive outer retinal necrosis (PORN). The complications are optic nerve sheath effusion and retinal detachment.

Toxoplasmosis

In immunocompetent individuals it presents usually as reactivation while in AIDS it occurs as a primary infection. Also in AIDS, it is more severe, bilateral, multifocal and not associated with chorioretinal scars. Its complications are iritis, vitritis, choroiditis, multifocal or diffuse necrotizing retinitis, papillitis, retrobulbar neuritis or outer retinal toxoplasmosis.

Pneumocystis and Cryptococcal Choroiditis

Pneumocystis carinii causes choroiditis which is bilateral and multifocal and may be associated with conjunctivitis, orbital mass and optic neuropathy. Cryptococcal choroiditis presents as solitary, multifocal or confluent which may be associated with eyelid nodule, conjunctival mass, iritis, vitritis, retinitis, and optic neuritis.

Tuberculosis

Although systemic tuberculosis is the most common opportunistic infection in AIDS, ocular tuberculosis is very rare. It presents as multifocal choroid tubercle with complication of exudative retinal detachment. There has been a changing trend with worsening of its clinical features post HAART.

Malignancies

Non Hodgkins Lymphoma (NHL) manifests as retinitis, choroiditis, retinal vasculitis, vitritis, subretinal mass, and uveitis.

Neuro ophthalmic complications

In AIDS patients, the neuro ophthalmic complications occur as perineuritis, retrobulbar neuritis, papilledema, papillitis or optic atrophy. It is usually a secondary manifestation of infection or lymphoma involving brain and meninges.

Syphilis

In AIDS patients, syphilis presents as vitritis, retrobulbar optic neuritis, perineuritis, neuroretinitis, papillitis, retinal vasculitis, or necrotizing retinitis.
Summary:
AIDS leads to a wide spectrum of ophthalmic manifestations which can be vision threatening with a potential to hamper the quality of life. There has been a profound impact on the clinical presentation of AIDS after the advent of HAART. HAART has definitely played a crucial role in reducing the severity and aggressive course of kaposi sarcoma and squamous cell carcinoma and several opportunistic infections but HZO is still very common. Post HAART, the incidence of CMV retinitis and its attendant complication retinal detachment has been considerably reduced. Moreover, once HAART improves the CD4 cell count, the anti-CMV therapy can be discontinued. Paradoxically, HAART has led to a new vision threatening spectrum due to immune recovery phenomenon encompassing anterior uveitis, vitritis and cystoid macular oedema. There is a need for the ophthalmologist to be aware of these changing trends in post HAART era in AIDS patients for their correct diagnosis and proper management.

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