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Review article

Opportunistic ocular infections in AIDS

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Abstract

As the number of HIV infected patients is multiplying exponentially day by day so are the associated ocular complications. The increasing longevity of individuals with HIV disease has resulted in greater numbers of patients with ocular opportunistic infection. By the means of this article we describe various opportunistic ocular infections in AIDS and their clinical manifestations, discussed under four headings; 1) adnexal manifestation; 2) anterior segment manifestation; 3) posterior segment manifestation; 4) neuro ophthalmic manifestation. Herpes zoster ophthalmicus, molluscum contagiosum and Kaposi sarcoma are common adnexal manifestations. Molluscum contagiosum being the commonest. Varicella Zoster Virus (VZV) and herpes simplex virus (HSV) most commonly cause infectious keratitis in HIV-positive patients. As compared to the immunocompetent individuals the frequency of bacterial and fungal keratitis is not more in HIV patients, but it tends to be more severe. Posterior segment structures involved in HIV-positive patients include the retina, choroid, and optic nerve head. The herpesvirus family is implicated most commonly in infections of the retina and choroid in HIV positive patients. CMV is the most common cause of retinitis and the commonest intraocular infection in AIDS. Atypical presentations resistance to conventional treatment and higher rate of recurrence make the diagnosis and therapeutic intervention more difficult and challenging. In addition, in one eye, several infections may occur at the same time, rendering the situation more difficult.

Keywords: human immunodeficiency virus(HIV); acquired immunodeficiency syndrome(AIDS); eyes

INTRODUCTION

More than forty million individuals carry the HIV worldwide. Among the individuals infected with HIV, approximately 70-80% experience ocular complications during the course of the disease. As the rate of ocular involvement in HIV is very high, a regular screening of seropositive is necessary to allow early identification of potential vision threatening disease. In general, CD4 + T-lymphocyte count has been used to predict the onset of certain ocular infections in HIV positive patients. CD4 + T-cell count less than 500 cells/mm^3 is associated with Kaposi sarcoma, lymphoma, and tuberculosis; CD4 + T-cell count less than 250 cells/mm^3 is associated with pneumocystosis and toxoplasmosis; and CD4 + T-cell count less than 100 cells/mm^3 is associated with retinal or conjunctival microvasculopathy, cytomegalovirus (CMV) retinitis, varicella-zoster virus (VZV) retinitis, mycobacterium avium complex infection, cryptococcosis, microsporidiosis, HIV encephalopathy, and progressive multifocal leukoencephalopathy. Atypical presentations resistance to conventional treatment and higher rate of recurrence make the diagnosis and therapeutic intervention more difficult and challenging. We here describe the common ocular opportunistic infections in HIV positive patients discussed under four categories: 1) adnexal manifestation; 2) anterior segment manifestation; 3) posterior segment manifestation; 4) neuro oph-

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thalmic manifestation .

Adnexal Manifestations

Ocular adnexa consist of the eyelid, the conjunctiva, and the lacrimal drainage system. Common ocular adnexal lesions in HIV positive patients include herpes zoster ophthalmicus (HZO), Kaposi sarcoma, molluscum contagiosum, and conjunctival microvasculopathy.

Herpes Zoster Ophthalmicus

HZO results from the reactivation of latent virus from a previous primary infection The commonest nerve involved is the ophthalmic division of trigeminal nerve. Herpes zoster ophthalmicus (HZO) is characterized by a vesiculobullous rash in the dermatome of ophthalmic branch of the trigeminal nerve and may be associated with keratitis, conjunctivitis, blepharitis, uveitis. Retinitis and Optic neuritis[1,2] HZO affects about 5-15% of patients who are infected with HIV. The most common predisposing factor for herpes zoster infection is age commonly affects individuals in the sixth and seventh decades of life. A high correlation of HZO in young patients and HIV is seen in various studies. It may be an initial manifestation of HIV infection in young persons[3,4] HIV infection appeared to correlate with more severe corneal involvement and postherpetic neuralgia[5]. Treatment includes Intravenous acyclovir 10 mg/kg 3 times per day for 7 days, followed by oral acyclovir 800 mg to 1 g 3-5 times per day for an additional 7 days. This regimen is most effective when started within 72 hours of onset of the vesicular lesions

Kaposi Sarcoma

Kaposi sarcoma is a mesenchymal derived vascularized tumor affecting the skin and mucous membranes. In approximately 20% of individuals with HIV-associated Kaposi sarcoma , the tumor involves the eyelids, conjunctiva, and, in rare cases, the orbit1 . This tumor is caused by human herpesvirus type 8. It is seen commonly in patients who are infected with HIV. Radiation therapy, Local cryotherapy, Intralesional chemotherapy and Surgical excision are various modalities of treatment for KS

Molluscum Contagiosum

Molluscum contagiosum is the most common AIDS associated adnexal manifestation. Molluscum contagiosum is caused by a DNA poxvirus, which spreads by direct contact with infected persons or by fomites 1. Manifested as small, painless, umbilicated lesions over the eyelids with associated toxic keratoconjunctivitis. Molluscum contagiosum is more frequent, severe and resistant to conventional treatment in HIV positive patient than in immunocompetent patients.

Anterior Segment Manifestations

Varicella Zoster Virus (VZV) and herpes simplex virus (HSV) most commonly cause infectious keratitis in HIV-positive patients Atypical presentation , higher rate of recurrence and resistance to treatment is encountered in HIV patients. As compared to the immunocompetent individuals the frequency of bacterial and fungal keratitis is not more in HIV patients, but it tends to be more severe. The most common organism is candidal species, especially in intravenous drug users. Microsporidia a protozoa is another important opportunistic infection in HIV-positive patients

Herpes Simplex Virus Keratitis

HSV is a DNA virus that often infects humans. Two strains of HSV exist herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2) HSV infection is spread by direct contact with infectious secretions from infected carriers. HSV-1 commonly is responsible for oral and ocular infections, while HSV-2 is responsible for genital infections. However, some cases of HSV-2 causing oral or ocular infections and HSV-1 causing genital infections have been reported. Similar to VZV, HSV can remain dormant after primary infection with subsequent reactivation in immunocompromised state. Following reactivation, HSV is transported down the nerve axon to the epithelial cells on the ocular surface or cornea. About 0.15% of the population has a history of external ocular HSV infection. Approximately 67% of patients with HSV infections develop epithelial keratitis. Prevalence of HSV keratitis is higher in patients who are infected with HIV compared to the general popu-

lation Treatment consists of trifluorothymidine and cycloplegic drugs, with debridement of the ulcer using a cotton-tip applicator. Oral acyclovir (400 mg twice daily for 1 year) decreases the risk of recurrent HSV keratitis by 50%[6].

Fungal Keratitis

Candidal species are the most common fungal organisms causing keratitis in HIV-positive patients especially in intravenous drug users[7,8]. Other fungal organisms known to cause keratitis includes Fusarium or Aspergillus species Immunosuppression predisposes HIV-positive patients to infection by nonfilamentous fungus. The filamentous fungi (eg, Fusarium or Aspergillus species) are seen in association with trauma with vegetable matter the incidence of these in infectious keratitis is same as in immunocompetent individuals.

Microsporidia

Microsporidia has emerged as an important opportunistic infectious protozoon in HIV-positive patients. Immunosuppression predisposes patients who are HIV positive to infection by microsporidia, which are intracellular parasites capable of causing corneal and conjunctival infection. Microsporidia corneal or conjunctival infection is very rare in immunocompetent individuals. Microsporidia is very difficult to culture, but it is seen readily within corneal or conjunctival epithelial cells with the use of Masson trichrome or Giemsa stain. Topical fumagillin has been used successfully to treat keratoconjunctivitis secondary to Microsporidia

Iridocyclitis

Iridocyclitis in patients who are HIV positive tends to be mild and often is associated with retinitis due to CMV or VZV. When iridocyclitis is severe, it usually is seen in association with ocular toxoplasmosis, tuberculosis, syphilis, or bacterial or fungal retinitis (rare). Other causes of iridocyclitis in HIV-positive patients include medications (eg, rifabutin, cidofovir). The etiology of iridocyclitis in HIV-positive patients includes sequelae of retinitis, retinochoroiditis, and drug toxicity. More frequently its occurrence is usually in association with HSV and VZV infections.

Posterior Segment Manifestations

Posterior segment structures involved in HIV-positive patients include the retina, choroid, and optic nerve head. Disorders of at least one of these structures are seen in more than 50% of patients who are HIV positive. Common presenting complaints include floaters, flashing lights, visual field defect, and decreased visual acuity. Diagnoses often are based on clinical evidence seen on funduscopic examinations. The herpesvirus family is implicated most commonly in infections of the retina and choroid in HIV positive patients. These viruses are obligate intracellular parasites and can cause damage the retina and choroid, either by direct invasion or by altering the host immune system. CMV is the most common cause of retinitis and the commonest intraocular infection in AIDS. VZV and HSV are said to be responsible for acute retinal necrosis (ARN), while VZV is the proposed etiology of progressive outer retinal necrosis (PORN) a form of necrotizing retinitis. Common bacterial causes of retinitis in HIV positive patients include Treponema Pallidum (syphilis) and Mycobacterium Tuberculosis. Fungal causes of retinitis and/or choroiditis include Cryptoccocus neoformans, Histoplasma capsulatum, and Candida and Aspergillus species. While parasitic causes include Toxoplasma gondii and Pneumocystis carinii.

Cytomegalovirus Retinitis

This is the most common cause of intraocular infection in patients with AIDS occurring in about 15-40% patients. CMV is predominantly transmitted perinatally in the neonates. In childhood, the major mode of transmission is by close contact, while in adults it is mostly transmitted through sexual contact or blood transfusion. Primary infection by CMV usually is asymptomatic. The reactivated CMV infection is responsible for the vision and life-threatening complications of this infection. Reactivation of the latent CMV commonly is seen in the immunocompromised host, especially HIV-infected patients with a CD4count less than 100 cells/ml Clinically, lesions commonly appear within the retina as multiple granular white dots with varying amounts of hemorrhage Other findings associated with CMV retinitis include

perivasculitis, vascular attenuation, vessel closure[13,16], vitritis, anterior uveitis, and papillitis[17,18] With the introduction of effective ART, the incidence of CMV retinitis has been noted to decrease by about 75%. CMV retinitis usually responds to initial therapy, the prompt recognition of recurrent CMV retinitis is of particular importance. The drug of choice for the treatment of CMV retinitis depends on the extent and location of the disease, possible drug-related side effects, and effectiveness of prior treatments. Specific agents and modalities for the treatment of CMV retinitis include the following oral, intravenous, and intravitreal ganciclovir; intravenous and intravitreal foscarnet or combined intravenous ganciclovir and foscarnet; or intravenous cidofovir.

Acute Retinal Necrosis

ARN is a fulminant retinal vaso-occlusive necrotizing retinitis. Patients with ARN tends to have a CD4 + count greater than 60 cells/mL, usually with a history of VZV or HSV dermatitis. The underlying pathophysiologic mechanism for causing ARN rests on the virulence of these viruses following their reactivation and the severity of ARN depends on the degree of the patient´s immunocompromise. Generally, VZV has been associated more frequently with ARN compared to HSV and CMV infections. Incidence of VZV-associated retinitis after HZO in HIV positive patients is 4-17%. Although course and severity is same irrespective of the virus responsible. For reasons unknown ARV is twice more common in males than in females. Intravenous or intravitreal ganciclovir or foscarnet are the treatment of choice.

Progressive Outer Retinal Necrosis

PORN is a rapidly progressive, necrotizing retinitis that has been reported in patients with advanced AIDS. The exact pathophysiologic mechanism for PORN has not been elucidated completely, the general consensus is that severe immunocompromise along with a previous infection with VZV are necessary. PORN also has been described in patients with severe immunocompromise secondary to chemotherapy. Incidence of PORN is much lower than ARN.

Syphilis

Syphilis results from the proliferation and infiltration of Treponema pallidum into ocular structures. Histologic study demonstrates mononuclear and polymorphonuclear cell infiltration of the involved ocular tissue, particularly cornea, iris, retina, and choroid. Ocular involvement may be unilateral or bilateral and but central nervous system (CNS) involvement is seen in up to 85% of patients[9,10]. A modification of the host response to syphilis in HIV-infected patients may occur, which is partly responsible for the rapid course of CNS involvement in these patients. Syphilis can run a more rapid and aggressive course in HIV-infected patients than in immunocompetent individuals[11,12] Incidence of syphilis has been on the rise since 1985 and about 30-40% of all the new cases were homosexual and bisexual males Administration of intravenous penicillin for longer periods resulted in improvement of vision in HIV-positive patients with ocular syphilis. Some authors have recommended that all HIV-positive patients with ocular syphilis be treated with the antibiotic regimen for neurosyphilis (12-24 million units of aqueous penicillin G given intravenously for a minimum of 10 days)[11].

Tuberculosis

Reactivation of quiescent tubercle bacilli as a result of the immunocompromised condition of the host account for close to 90% of new cases of ocular tuberculosis. Tuberculosis represents a significant cause of granulomatous uveitis in patients who are HIV positive. Approximately 90% of the new cases result from the reactivation of the latent tubercle bacilli in previously infected individuals. A recent increase in the incidence of TB is closely correlated to the HIV infection . It is one of the commonest opportunistic infection in AIDS.

Pneumocystis carinii Choroidopathy

Infectious choroiditis comprises less than 1% of ocular disorders in HIV-positive patients, with P. carinii as the most common identified organism. P. carinii choroidopathy tends to occur in immunocompromised hosts, particularly HIV patients with disseminated infection. An increased association with use of aerosolized pentamidine prophylaxis has occurred. Multiple choroidal lesions pale yellow-white in col-

our, round or ovoid of variable sizes, usually in both eyes, clinically characterize Pneumocystis choroiditis[22]. The lesions may coalesce to form large regions of confluent involvement with resultant choroidal necrosis foveal involvement during[4,21] this process may lead to loss of central vision[21].

Toxoplasma Retinochoroiditis

Toxoplasmosis is the most common cause of retinochoroiditis. Infection with T. gondii may be congenital or acquired. Ocular manifestation is usually preceded by systemic disease. T. gondii is an intestinal parasite in cats. Infection in humans may occur either by inhalation or by ingestion of oocysts by consuming poorly cooked meat or unpasteurized milk that has been infested with the organism. In general, toxoplasma infection is well tolerated in most tissues of the body, except the eyes. T. gondii may remain as bradyzoites within an inactive chorioretinal scar until reactivated as a result of immunosuppression. The exact mechanism of reactivation has not been elucidated completely but probably it is the transformation of the bradyzoites into tachyzoites that allows for new infection of the retina and choroid, leading to recurrent retinochoroiditis. Toxoplasmosis is the most common cause of retinochoroiditis, accounting for about 30-50% of all posterior uveitis[1].

Histoplasma Chorioretinitis

H. capsulatum gram-positive, mycelial dimorphic fungus, is endemic particularly the Mississippi-Ohio River Valley. The organism enters the body via the respiratory tract by inhalation of spores. Acute histoplasmosis tends to be benign and self-limiting, mostly affecting the pulmonary system. The organism often is spread hematogenously producing lesions throughout the body, especially in the reticuloendothelial system of the liver, spleen, lymph nodes, and bone marrow. This also may take a subclinical route. Disseminated histoplasmosis is uncommon in healthy adults without any immunologic defects. Risk factors contributing to the dissemination of infection include a defective immune system, such as seen in AIDS or malignancies, immature immune system in infants, or iatrogenic immunosuppression. This disease tends to have a fulminant course, usually complicated by disseminated intravascular coagulation with high mortality rate.

Cryptococcal Chorioretinitis

C. neoformans yeastlike fungus with a world wide distribution[23]. Its infection is most frequently acquired from pigeon or other bird droppings although the organism has been isolated from soil, fruit, and milk. As the Cryptococcal infection occurs by inhalation of airborne spores it initially remain in the lungs and then hematogenously spread to other parts of the body. This organism has predilection for the brain and meninges. Intraocular infection may occur either via direct extension from the CNS or through the hematogenous route mostly in immunocompromised or debilitated patients CNS involvement with Cryptococcus in HIV-infected patients is relatively common and often results in meningitis with secondary ocular findings[15] Choroiditis and chorioretinitis from cryptococcal infection also have been observed in HIV-infected patients[14, 15, 20]

Candida endophthalmitis

Typical candidal fungal lesions appear as fluffy white "mounds," forming string of pearl appearance which are frequently bilateral and superficially located, and often extend into the vitreous. There usually is an overlying vitritis, and vitreous abscesses also may be seen[19] Candida retinitis is not commonly seen in HIV-infected patients, but may be more likely in the setting of intravenous sources of infection as well as through indwelling catheters

Neuro ophthalmic manifestations

The common causes of neuro-ophthalmologic complications include cryptococcal meningitis, neurosyphilis, and toxoplasmosis. More diffuse encephalopathy may be due to either direct effects of the virus (HIV retinopathy) or to superimposed infection from Polyma virus causing progressive multifocal leukoencephalopathy (PML). Neuro-ophthalmologic complications are seen in approximately 10-15% of patients who are infected with HIV.

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