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Ophthalmic Manifestation of CMV in HIV Infection

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ABSTRACT

Ocular complications are common manifestations in HIV/AIDS patients. Cytomegalovirus retinitis (CMV-R) and Herpes zoster ophthalmicus are the two most common ocular complications. With the advent of highly active anti-retroviral therapy (HAART), CMV-R has declined considerably in the western world, but it is still possesses a major challenge in developing countries with significant ocular morbidity. CMV-R usually involves anterior segment and retina, manifesting as confluent retinal necrosis with haemorrhage, granular lesion, and frosted branch angiitis. The clinical picture of HIV-associated eye disease has changed dramatically since the introduction of HAART. It can lead to severe complications at times like rhegmatogenous retinal detachment and vision loss. Management of CMV Retinitis is more challenging and continuously evolving with time. Currently available effective anti-CMV pharmacological agents include injectable ganciclovir, its prodrug valganciclovir, and foscarnet. Surgical management of the complications include various approaches like pars plana vitrectomy (PPV) with gas or high viscosity silicone oil tamponad, scleral buckling and laser photocoagulation. Because of the varied clinical presentation and difficult course, CMV-R has established itself as the major determinant of visual morbidity in HIV/AIDS patients. Therefore with the introduction of newer screening methods and routine ocular examination in high risk groups, we can significantly reduce the burden of disease, severe ocular complications and ocular morbidity.

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Introduction

Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) is an impaired immune system disease with global burden. It has become an important indicator of the worldwide morbidity and mortality in the recent time. There are about estimated 34 million people worldwide with HIV/AIDS. HIV destroys the CD4 helper T-cells leading to increased incidence of opportunistic infections. Opportunistic infections are a major cause of mortality and morbidity in HIV/AIDS patients. Various microorganisms are associated with HIV led opportunistic infection, out of which cytomegalovirus (CMV) can lead to severe visual morbidity.

HIV and Ocular Diseases

Ocular complications are common manifestation in infected individuals with at least 50–75% of infected individuals expected to develop ocular disease at some point of time during the course of the disease progression. A 10 year retrospective study^[1] conducted in HIV/AIDS patients for its ocular manifestation, noted varied patterns of ocular involvement, ranging from external eye involvement to severe retinal disease and microangiopathy. The opportunistic HIV ocular diseases mainly comprises of Cytomegalovirus retinitis (CMV-R), herpes simplex keratitis, Varicella Zoster

ophthalmicus, Toxoplasma retinitis to Pneumocystis carinii choroidopathy. The two most common ocular involvements in HIV positive patient are: CMV-R and Herpes zoster ophthalmicus. But with the increase in overall HIV positive cases, there is a constant rise in the CMV-R and it possesses a significant threat to ocular morbidity.^[2]

The involvement of anterior segment is more common than the posterior segment. The ocular manifestation in HIV/AIDS is directly related with the overall CD4 count. HIV/AIDS patients developing the posterior segment disease have lower CD4 as compared to the anterior segment. Increased age is another very important predictor of ocular involvement in these patients.^[3]

Cytomegalovirus in HIV

Cytomegalovirus is the most common cause of blindness in HIV/AIDS. It is expected that about 10% to 20% of HIV positive patient becomes blind worldwide due to CMV infection and its related complications. CMV commonly involved retina causing retinitis and can lead to severe complication like: retinal detachment and vision loss. These ocular complications are common in HIV positive patients as compared to the HIV negative people.^{[4][5]} Although with the advent of HAART, HIV and AIDS-related morbidity and mortality have drastically decreased in the developed world.

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This decrease in mortality and morbidity supersedes the complication of HAART and is the most effective agent to control the progression of AIDS and related complication. Despite chances of potential complications, HAART was able to decrease the incidence of AIDS and overall AIDS related mortality. Because of this HAART remains the gold standard for the HIV treatment, halting its progression.^{[6][7][8]} But it still continues unabated in the developing countries, partly due to economical, social reason aided by emergence of drug resistance.

Anterior Segment Manifestation

Although anterior segment is not commonly affected in CMV infection, it can be a cause of significant ocular handicap in the HIV/AIDS patients. With the use of HAART and increased survival, the anterior segment involvement has become a problem for the HIV/AIDS patient and clinicians.^[9]

CMV can be transmitted by blood, saliva, breast milk, and mucous membrane contact. It can produce transient conjunctivitis, iritis^[10], epithelial and stromal keratitis^[11], endothelialitis^[12,13], anterior uveitis^{[14],[15]}, sectoral iris atrophy^[16] and secondary glaucoma^[17]. The endothelialitis appear as linear or stellate lesions and form a reticular pattern^[13].

Posterior Segment Manifestation:

Posterior segment involvement is the most common eye manifestation in HIV/AIDS. Most of these patients will have retinal involvement with retinitis and chorioretinitis, followed by retinal microangiopathy.^[18] The involvement of posterior segment will cause more debilitation disease and potentially lead to loss of vision in comparison with the anterior segment. The posterior segment involvement of HIV/AIDS by CMV can cause retinitis and subsequent retinal detachment^[19].

Cytomegalovirus retinitis used to affect up to 40 to 50% of AIDS patients prior to HAART.^[20] With the advent of HAART it has declined considerably in the western world, but not in the developing countries.^[21] In India, CMV retinitis still remains the commonest ocular manifestation in HIV AIDS cases.^{[22][23]} It may be unilateral to start with, but up to 50% ill eventually develop bilateral disease^[24]. The overall damage to the posterior segment and related structure can be due to direct effect of the virus or by increased host immune response. These patients can have vitritis and can progress into severe macular edema.^[25] Cytomegalovirus retinitis occurs almost exclusively in patients whose CD4+ counts are <50 cells/ μ L.^[26]

Clinical findings

There are three clinical forms of CMV retinitis:

Classical form

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.

Indolent form

In contrast, the indolent form is recognized as a granular lesion in the peripheral retina, often with little or no hemorrhage which may lead to floaters.

A third uncommon presentation is frosted branch angiitis. Due to possible indolent form, high degree of suspicion is required for the early diagnosis of CMV retinitis and subsequent prevention of complication. Therefore routine screening with dilated indirect ophthalmoscopy has been recommended at three-month intervals in patients with CD4+ counts less than 50 cells/ μ L.^[27]

Cytomegalovirus retinitis may result in either serous or rhegmatogenous retinal detachment which may occur during the active or even 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.^[28] But in developing countries, the incidence of CMV-related retinal detachment is found to have increased.^[24]

Management

Management of CMV Retinitis is more challenging and continuously evolving with time and recent advancements in medical technologies. The management includes various approaches like pars plana vitrectomy (PPV) with gas or high viscosity silicone oil tamponade (preferably 5000 centi stokes), scleral buckling and laser photocoagulation. Scleral buckling and laser photocoagulation have been effective in the repair of retinal detachments related to CMV retinitis.^[29] But the treatment of CMV retinitis needs to be individualized depending upon the location of the active retinitis and the immune status of the patient.

Currently available anti-CMV agents include injectable ganciclovir, its prodrug valganciclovir, foscarnet, cidofovir, fomivirsen, ganciclovir and intraocular implant. The clinical picture of HIV-associated eye disease has changed dramatically since the introduction of HAART.^[30] There are also reported cases of CMV-R resistant to ganciclovir due to A594V and L595W mutations. These findings can be related to an overall impact of multiple other confounding factors as repeated ganciclovir use, increased initial viral load and decreased CD4. But it does warrant for us the emergence of drug resistant CMV emergence and further understandings of it.^[31]

Although direct infectious destruction of tissue is less severe, inflammatory infiltration is augmented, and this gives rise to a situation that is open to misinterpretation. Before the introduction of protease inhibitors, patients with CMV retinitis typically had CD4 T-lymphocyte counts less than 50 cells/cu.mm with minimal intraocular inflammation.^{[32][33]} Significant intraocular inflammation has now been reported in some patients with CMV retinitis who have had improved immune function with HAART. Immune recovery uveitis, which involves mainly the anterior uvea and vitreous, is often associated with a marked disturbance of visual function.^{[34][35]} Hence it is important to identify the occurrence of this phenomenon early in patients on HAART on their path to immune recovery.

Based on the higher incidence and prevalence of HIV related CMV retinitis and other ocular complications, routine screening is recommended in HIV positive patient. Routine screening has higher significant in patient with CD4 count less than 200 cells/ μ L, due to high prevalence of ocular diseases in this group. Similarly routine screening is also helpful to detect occult ocular infections, which is fairly common in CMV retinitis and other diseases.^[36]

Conclusion

CMV related ocular diseases are one of the most common ocular manifestations of HIV/AIDS patients. The early diagnosis and treatment of CM retinitis still possess a challenge due to its varied presentation and indolent form. With the recent advancement of HAART and other new anti-retroviral drugs, although the overall incidence of ocular involvement is decreasing, there is still rise in CMV retinitis in developing countries. Therefore with the introduction of newer screening methods and routine ocular examination

added with subsequent early treatment in high risk groups and HIV positive patient, we can significantly reduce the burden of disease, severe ocular complications and ocular morbidity associated with HIV/AIDS.

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