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The Changing Pattern of Cytomegalovirus Retinitis in Human Immunodeficiency Virus Disease

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ABSTRACT

There have been profound changes in the pattern of cytomegalovirus (CMV) retinitis over the last two decades. The epidemiology and behaviour of CMV retinitis has been significantly altered by Acquired Immune Deficiency Syndrome (AIDS). It was uncommon prior to the AIDS epidemic, but soon became the most common retinal infection in AIDS patients. In the past several years, highly active anti-retroviral treatment (HAART) has achieved a dramatic improvement in the prognosis for patients infected with human immunodeficiency virus (HIV). As a result, HIV patients are living longer and have a reduced risk of CMV retinitis. Some patients with CMV retinitis who respond to HAART develop a transient symptomatic vitritis while others undergo no reactivation of their retinitis despite having no specific anti-CMV therapy. This pattern is likely to undergo further change as the treatment of HIV and CMV disease continues to improve.

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Ophthalmology, like so many other fields of medicine, has undergone momentous change since the early reports of Acquired Immune Deficiency Syndrome (AIDS) and its ophthalmic complications[1-3]. The immunocompromised state associated with AIDS patients has resulted in a variety of previously rare infections and neoplasms that affect the eye and its adnexae. AIDS has significantly altered the epidemiology and behaviour of some of these diseases. Among them, the changing pattern of cytomegalovirus (CMV) retinitis has been particularly dramatic.

Although serological studies indicate that previous exposure to CMV has occurred in a large proportion of the adult population, CMV does not cause clinically apparent disease in most cases[4]. CMV infection of the eye can, however, occur in congenitally infected newborns, and in immunocompromised individuals such as those with organ transplant on immunosuppressive drugs[4,5].

Prior to the AIDS epidemic, CMV infection of the retina in adults was uncommon. The first confirmed case of this viral retinitis in an adult was reported by Smith in 1964[4,6]. The patient was a 61-year-old woman who had been treated with chemotherapy for Hodgkin disease. Moeller and co-workers were able to identify less than 50 reported cases in the English language literature of CMV retinitis in patients with acquired CMV disease in 1982[7].

CMV retinitis was first described in association with AIDS patients in 1982[2,8], and soon became recognised as the most common retinal infection in these patients[3,9]. The incidence of CMV retinitis is higher among immunocompromised patients with AIDS than among those following organ or bone marrow transplantation.

The diagnosis of CMV retinitis is an important milestone for the AIDS patient because it represents a new degree of "immunosuppression"[10]. This is because CMV retinitis characteristically affects individuals with peripheral-blood CD4+ T-lymphocyte (CD4) counts less than 50 cells/μl, and is rarely seen in those with counts more than 200 cells/μl[5]. At the beginning of the epidemic, those diagnosed with this opportunistic infection were given only several months to live. In addition to the reduced life expectancy, these patients had to cope with blindness from the infection and its adverse effects on the quality of life[10].

In the past few years, a dramatic improvement in the prognosis for patients infected with the human immunodeficiency virus (HIV) has been achieved with the strategy of using a combination of anti-retroviral drugs to bring about a profound and durable suppression of viral replication[11]. Highly active anti-retroviral treatment (HAART), as it is often called, consists of a HIV protease inhibitor combined with one or two dideoxynucleoside agents (reverse transcriptase inhibitors). It dramatically increases absolute CD4 counts, reduces HIV viral load and improves survival, even in patients with very low CD4 counts[12]. As a result of HAART, HIV patients are living longer and have a reduced risk of opportunistic infections, including CMV retinitis. With improved life expectancy

of patients, the ophthalmologist's treatment goal has gradually evolved from maintaining vision in one eye until the patient's ultimate demise (previously after 3-4 months), to preserving good vision in both eyes for as long as possible.

Prior to the introduction of HAART, the natural history of untreated CMV retinitis in AIDS patients was relentless progression of full-thickness retinal necrosis leading to visual loss and blindness over about 6 months. The disease also tended to become bilateral[4,13], and spontaneous regression of retinitis without specific anti-CMV medication was thought never to occur[4]. With HAART regimens, cases of healed or regressed CMV retinitis have been reported in patients who have never had specific anti-CMV therapy[14,16].

Specific anti-CMV medications such as ganciclovir and forscarnet were previously given for life routinely to prevent disease reactivation because the drugs are only virustatic. As these drugs have to be administered intravenously (ganciclovir can be given orally but it has low bioavailability and is less efficacious than its intravenous form), long-term therapy is problematic in these immunocompromised patients because of the risk of life threatening sepsis. Furthermore, the presence of an indwelling catheter and the time required to infuse these medications reduce the patient's quality of life. It is now becoming clear that some patients with CMV retinitis who respond to HAART in terms of elevated CD4 count and reduced HIV viral load undergo no reactivation of their retinitis despite having no specific anti-CMV therapy[14-16]. The ability to substitute close ophthalmologic observation and CD4 count monitoring for long term intravenous anti-CMV therapy is clearly advantageous, and this is possible in some patients with quiescent CMV retinitis and sustained HAART-induced CD4 count elevation. The factors underlying this HAART-induced improved immunity are still not entirely clear. Although most cases of HAART-induced spontaneous and sustained resolution of CMV retinitis had elevated CD4 counts, sustained regression of this viral infection has been reported in one patient with a persistently low CD4 count.

The incidence of CMV retinitis has been documented to be at least 25% of patients with advanced AIDS[4]. However, this incidence has declined dramatically among patients maintained on HAART. In the United States where 86% of the 240,000 HIV patients receive HAART, the incidence of CMV retinitis has dropped to just 3.3% in 1998[18].

One of the features that has characterised CMV retinitis in patients with AIDS is the lack of inflammation in the anterior chamber and vitreous humour[19]. Indeed, the presence of marked vitreous inflammation is often used to discriminate between CMV retinitis and other causes of retinitis in patients with AIDS, such as toxoplasmic retinochoroiditis. A transient symptomatic vitritis has now been observed in patients with AIDS and CMV retinitis receiving HAART[20], and cystoid macular oedema and epiretinal membrane formation have been reported in association with this vitreous inflammatory reaction. Presumably, this inflammation reflects an improved immune response against CMV. It can be treated with systemic or repository corticosteroid with visual improvement but without reactivation of the retinitis. The term immune recovery vitritis has been applied to this new syndrome[21].

In summary, we have witnessed profound changes in the pattern of CMV retinitis over the last 2 decades. It is clear that HAART has completely changed the landscape of HIV disease, as well as the behaviour and treatment of CMV retinitis. As the treatment of HIV and CMV disease continues to improve, the pattern of CMV retinitis is likely to undergo further change. Clinicians should therefore remain vigilant to the changing pattern of this disease.

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