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Review of Cytomegalovirus Anterior Uveitis

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1. Introduction

Cytomegalovirus (CMV), a member of the herpes family which includes herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), and Epstein-Barr virus (EBV), is ubiquitous worldwide. About 85% of persons above the age of 40 in the general community are seropositive.[1] CMV infections manifest more usually in immunocompromised individuals especially in patients with acquired immune deficiency syndrome (AIDS); however more recently, CMV infections have been reported in the immunocompetent person, manifesting as corneal endotheliitis as well as anterior uveitis associated with elevated intraocular pressure (IOP; hypertensive anterior uveitis).[2-8] This chapter aims to review the ocular features and treatment of CMV anterior uveitis in the immunocompetent person.

2. Pathophysiology

Viruses are increasingly being implicated as a cause of what was previously considered to be idiopathic ocular inflammations in immunocompetent patients. CMV and HSV have been associated with Possner-Schlossman Syndrome (PSS)[4,9,10] and rubella and HSV have been associated with Fuchs Heterochromic Iridocyclitis (FHI).[11-13] In various studies, the presence of CMV deoxyribonucleic acid (DNA) has been identified in 41.7% of FHI and 52.8% of PSS eyes.[14]

The overlap between the different viruses and the variability in clinical presentations do suggest that ocular manifestations of viral diseases in immunocompetent patients may not be specific to a particular virus but rather a response to the viral infection based on the individual's genetic make-up and immune status.[14]

These viruses share common characteristics. The core contains a linear double-stranded DNA, which is surrounded by a capsid and an envelope. The envelope is a derivative of the core membrane of the infected cells and consists of lipids with inserted viral glycoprotein. There are specific receptors of the glycoproteins of the envelope that recognize complementary receptors on the host cell membrane and bind to them by adsorption. The envelope and the cell membrane fuse while the viral nucleocapsid enters the cell. The viral proteins are then produced in a cascade. The synthesis of DNA and assembly of capsid take place in the nucleus while the production of infected particles in the cytoplasm leads to destruction of the host cell.[15-16] Viral DNA has been detected in monocytes, dendritic cells, megakaryocytes, and myeloid progenitor cells in the bone marrow.

Herpetic viruses are well known for their ability to cause keratitis, anterior uveitis, scleritis, and retinitis.[17-19] Anterior uveitis is unilateral and typically has a chronic and/or recurrent character. Intraocular pressure (IOP) elevation, keratitis, endotheliitis, and stromal iris atrophy commonly accompany it. The iris stroma is infiltrated with lymphocytes, and an increase in IOP is typically seen on activation of the uveitis, probably due to an outflow obstruction. This outflow obstruction can be explained by both a viral trabeculitis with swelling of the trabecular cells and an obstruction of the trabecular meshwork by inflammatory debris.[18-19]

The pathogenesis of CMV uveitis, although not completely understood, is believed to include various mechanisms such as viral replication, ischemic vasculitis, lymphocytic infiltration of the iris stroma or intraocular nerves. In addition, persistent and recurrent viral infection may cause an inflammatory reaction manifested as uveitis, or can trigger the immune system itself against viral antigens, eventually causing tissue and organ inflammation and damage.[20-24]

3. Ocular features

CMV in the anterior segment is a newly described entity that occurs even in people who are not infected with the human immunodeficiency virus (HIV).

CMV infection can cause a spectrum of ocular manifestations, varying in severity from a mild self-limiting iritis with sector iris atrophy,[6] to features of PSS,[4-9] to the more chronic form resembling FHI, or even corneal endotheliitis.[7] Two common features seen in these eyes with CMV uveitis are elevated IOP and iris atrophy. These features are consistent with the finding of CMV in the smooth muscle cells of the iris, the ciliary body, and the endothelial cells of the Schlemm canal.[17]

In an analysis of published studies of non-HIV, CMV-associated anterior uveitis in immunocompetent patients, researchers found clinical presentations including endotheliitis, recurrent acute anterior uveitis and ocular hypertension, and chronic anterior uveitis.[12] Eyes with such CMV-associated anterior uveitis usually have no corneal scars, no posterior synechiae, no flare or fibrin and no posterior segment involvement.

Corneal endotheliitis may be unilateral or bilateral, typically causes blurred vision and is associated with corneal edema, Descemet's folds, as well as fine and medium keratic precipitates that may be pigmented. Other associated clinical signs include iris atrophy, mild anterior chamber activity, reduced endothelial cell count, elevated IOP, coin-like lesions and the "owl eye sign" on confocal microscopy, representing inclusion bodies and macrophages.

As mentioned, CMV can present clinically as PSS or FHI. PSS and FHI are 2 separate clinical entities that are similar in some aspects, but yet have important distinguishing features. Both have elevated intraocular pressures during the episodes of acute iritis (hypertensive anterior uveitis). Both have only a mild non-granulomatous anterior chamber activity with no posterior synechiae formation. However, PSS is an acute, intermittent, recurrent glaucomatocyclitic crisis with few keratic precipitates, while FHI is a chronic iridocyclitis with diffuse, fine, stellate keratic precipitates and may have vitritis. Exact aetiology of both conditions is still arguable although the consensus is that they are attributable to viruses including CMV as mentioned above.

PSS is usually unilateral, with symptoms of redness, blurring, haloes and unilateral headache. Clinical features include elevated IOP, anterior chamber cells (grades ½ to 2+)

and fine to medium keratic precipitates either in a ring or linear pattern. Diffuse and patchy iris stromal atrophy is common.

FHI may be unilateral or bilateral. The main symptom is blurred vision. Clinical features include elevated IOP, anterior chamber cells (grades 1 to 2+), fine feathery, diffuse keratic precipitates and diffuse "moth-eaten" iris atrophy.

From literature data to date, 110 eyes of 106 non-HIV positive patients with CMV anterior segment infection have been described[4-9] of which 27 eyes of 24 patients had endotheliitis, 57 eyes had acute recurrent anterior uveitis and the remaining had chronic anterior uveitis. All the 83 anterior uveitis eyes and 24 of the endotheliitis eyes had ocular hypertension.

4. Diagnosis

The usefulness of aqueous humor sampling has been established in both anterior uveitis and posterior uveitis. A number of recent studies have shown the benefit of aqueous humor polymerase chain reaction (PCR) for the diagnosis of infectious uveitis and revealed a good degree of concordance between intraocular antibody and real-time PCR. Testing for DNA tends to be positive at the outset (and/or early at reactivation) and antibody testing can be positive at any point in time.[25] A positive test result indicates at the most that the virus may be involved, but is by no means conclusive. A negative test does not exclude the herpes virus as a cause of the uveitis either.

A minimum of 100 µl aqueous should be obtained via a diagnostic anterior chamber paracentesis and the samples must be delivered to the laboratory at 18 to 25 degrees Celsius within one hour or stored and transported at 2 to 4 degrees Celsius within 24 hours. The samples should be aliquoted immediately on arrival at the laboratory and used for DNA extraction immediately or kept at −20 degrees Celsius and used for DNA extraction within one week.

Diagnostic anterior chamber paracentesis should involve the use of a 27-gauge needle inserted into the temporal, perilimbal, inferior one-third of the cornea; directed downwards while avoiding the lens. This has been shown to be a simple and safe office procedure.[26] Identification of the CMV virus makes it possible to institute the appropriate antiviral medication.

5. Treatment

Management of CMV anterior uveitis may involve the use of topical non-steroidal anti-inflammatory agents, topical steroids, topical anti-glaucoma medications and topical or systemic antivirals. Patients should also be co-managed by the infectious disease physician to exclude systemic cytomegalovirus infections and other forms of immunocompromised states.

Topical non-steroidal anti-inflammatory agents have been employed in the immediate setting to reduce ocular inflammation and treat the patient symptomatically. This is especially useful when the use of topical steroids is delayed intentionally till after the diagnostic anterior chamber paracentesis to allow better yield of viral DNA load when performing aqueous sampling.

Topical steroids alone may be able to reduce the inflammation and IOP in a minority of cases. More commonly, combination with anti-glaucoma medication will give rise to more

effective lowering of IOP. However, steroids may cause steroid-induced glaucoma as a side effect. This is especially seen in patients who are on steroids for a long duration.

Glaucoma therapy can be initiated in a stepwise manner in the following order, unless there are any contraindications to the medication: β-blocker, α-2 agonists, topical acetazolamide, and lastly, prostaglandin analogs. If the IOP exceeds 40 mm Hg, systemic acetazolamide can be considered. The medications when tailed down should be reduced in a stepwise manner as well, but in reverse order.

Mydriatics or cycloplegics can be used as an adjunct to relieve any ciliary spasm, stabilize the blood aqueous barrier and assist in fundal evaluation.

The main mode of antiviral therapy in these eyes has been systemic ganciclovir or valganciclovir.[5-8,14,27-28] Some authors have also used intravitreal injections of ganciclovir[28] or ganciclovir gel[14] with variable outcomes. In many cases, the inflammation resolved with therapy, only to recur on cessation of treatment.[5-7] Although there is no consensus as to which route of administration is most suitable, topical ganciclovir gel has been shown to produce less number of recurrences as compared to systemic gangciclovir.[29]

Response to therapy in eyes with chronic anterior uveitis can be defined as the clinical resolution of anterior chamber cells and keratic precipitates and good IOP control with or without glaucoma medications while on treatment. In eyes with acute recurrent anterior uveitis, response can be defined as absence of recurrence of inflammation and normalisation of IOP without glaucoma medications other than that given during the acute episode while on treatment.

All treated eyes responded to therapy, in terms of the severity of the inflammation and IOP control, to the initial antiviral treatment. However, 77.7% relapsed within eight months after stopping treatment, according to the experience of some authors.[6,29] This indicates that CMV anterior uveitis may require a longer period of treatment, perhaps similar to that of herpetic uveitis or even other methods of treatment.

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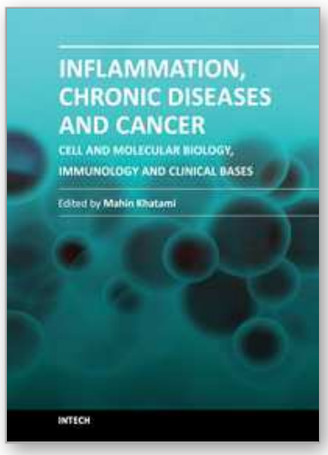
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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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