

Cytomegalovirus

Hypertensive iridocyclitis

E C Kim, T P Margolis

A new ocular presentation of cytomegalovirus?

The single most common diagnosis assigned to patients with uveitis is "idiopathic," and in a recent large epidemiological study 48% of new cases of uveitis were assigned this diagnosis.¹ However, with the development of new diagnostic technologies, the discovery of novel ocular pathogens, and the recognition that established ocular pathogens can present in previously unrecognised ways, fewer patients are now being diagnosed with "idiopathic" uveitis. Examples of novel ocular pathogens include *Bartonella henselae*,² *Borrelia burgdorferi*,³ West Nile virus,⁴ *Tropheryma whippelii*,⁵ microsporidia,⁶ *Baylisascaris procyonis*,⁷ and the leptospire.⁸ Examples of established ocular pathogens that can present in previously unrecognised ways include atypical presentations of toxoplasmosis,⁹⁻¹⁰ herpesviruses as the cause of the acute retinal necrosis syndrome¹¹⁻¹² and some cases of Posner-Schlossman syndrome,¹³ and varicella zoster virus as the cause of progressive outer retinal necrosis.¹⁴ In addition, two independent groups recently reported evidence linking rubella virus with Fuchs' heterochromic iridocyclitis.¹⁵⁻¹⁶ In the current issue of the *BJO* (p 846), de Shryver *et al* present evidence in support of cytomegalovirus (CMV) as a cause of hypertensive iritis in immune competent individuals.¹⁷

CMV is an extremely common human pathogen, infecting about 80% of the adult population.¹⁸ Following primary infection CMV establishes a lifelong latent infection in myeloid and dendritic cell progenitors.¹⁹⁻²⁰ Like the other herpesviruses, latent infection with CMV is characterised by a low level of viral gene transcription. However, in immune competent patients this chronic, latent infection is usually kept in check by a well established immune response, but recent studies indicate that in about a third of latently infected patients the infection is inefficiently controlled.²¹ For many years, it has been recognised that CMV can cause ocular disease in immune compromised individuals including neonates, transplant recipients, and patients with HIV/AIDS with low CD4 cell counts. CMV retinitis is slowly progressive, characterised by white infiltrates and retinal haemorrhage,

with progression that often follows the retinal vasculature. There may be an accompanying vitritis, and iritis. The iritis is characterised by fine stellate keratic precipitates distributed diffusely over the corneal endothelium.

There is compelling evidence to rethink the established paradigms about CMV ocular disease

Over the past 5 years, several groups have published case reports linking CMV to hypertensive iridocyclitis in four immune competent patients, a concept that challenges the current paradigm of CMV mediated ocular disease.²²⁻²⁴ The cumulative evidence for CMV as a causative agent in these cases included polymerase chain reaction (PCR) detection of viral DNA in the aqueous humour, local CMV specific antibody production, and clinical response to ganciclovir but not to aciclovir. However, all three lines of evidence were not obtained for any single clinical case reported. In the current issue of the *BJO*, de Shryver *et al* present more complete evidence linking CMV to hypertensive iridocyclitis in immune competent patients. In this case series, the authors present five cases of chronic or recurrent hypertensive iritis in immune competent individuals which previously would have been labelled "idiopathic," but which the authors provide credible evidence in support of CMV as the causative agent. CMV DNA was detected from the aqueous in five of five patients, but not from appropriate negative controls. A CMV specific antibody response was detected in the aqueous in four of four patients tested and therapy with ganciclovir, foscarnet, or valganciclovir led to resolution of inflammation in all five cases. Although one might be concerned that any of the above findings alone might represent a false positive result, the combination of all three lines of evidence provides compelling evidence to rethink the established paradigms about CMV ocular disease.

This challenge to established dogma arrives at a time when there is increased

recognition that CMV can be a cause of clinical disease in immune competent individuals. It is fairly well known that CMV is the most common cause of heterophile negative mononucleosis characterised by fever, malaise, liver function abnormalities, and an atypical lymphocytosis,²⁵⁻²⁶ but there are also a number of case series implicating CMV as a causative agent of meningitis, colitis, hepatitis, dermatitis, haemolytic anaemia, thrombocytopenia, and pneumonia in immune competent individuals.²⁷⁻³⁰ Furthermore, there is growing evidence of "subclinical" reactivation of latent CMV especially in the elderly³¹⁻³² and in patients with atopic disease,³³ and that chronic CMV immunological challenge leads to immune dysregulation, including altered cytokine profiles, chronic cell mediated inflammation, and reduced T cell diversity.³¹⁻³⁴ Is it possible that such alterations in immune surveillance and response could put a patient at even greater risk for developing non-infectious forms of uveitis?

An important point that de Shryver *et al* did not raise in their paper is the possibility that the CMV detected in the eyes of some, or all, of their patients might have been a consequence of local immunosuppressive therapy rather than the primary cause of their ocular inflammation. This possibility needs to be considered given that latent CMV is present in monocytes that transit through ocular tissues, especially in eyes with inflammation, and that this latent state is continuously, but inefficiently, regulated by the immune system.²¹ A recent case report by Saidel *et al* serves as an illustrative example of how local immune suppression can give rise to ocular CMV disease. In this report the authors described a case of CMV retinitis that developed in an immune competent diabetic patient following an intravitreal injection of triamcinolone acetonide for macular oedema.³⁵

With the growing awareness that CMV may cause hypertensive iridocyclitis and with the increased use of diagnostic testing of aqueous from eyes with uveitis, it is likely that more cases of CMV hypertensive iridocyclitis will soon be described. As this occurs the dual challenge to our profession will be to keep an open mind as well as be sharply critical of the evidence presented. We look forward to further studies and discussion on the topic of hypertensive iridocyclitis and the role that CMV may have in the pathogenesis of this condition.

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