

CASE REPORT

MOLECULAR DIAGNOSIS OF ACUTE RETINAL NECROSIS SECONDARY TO CYTOMEGALOVIRUS IN VITREOUS ASPIRATE

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Abstract. We report a case of a 45-year old Filipino post-kidney transplant patient maintained on steroids, who presented with floaters in her left eye. Vitreous aspirate was analyzed using polymerase chain reaction (PCR) for human cytomegalovirus (HCMV) and herpes simplex virus (HSV). A distinct band (435 bp) was found that confirmed the presence of HCMV. Since a rapid and accurate diagnosis is crucial for prompt administration of antiviral therapy, PCR-based analysis of vitreous aspirate provides a valuable tool in the diagnosis of patients with retinitis caused by herpes viruses.

INTRODUCTION

Acute retinal necrosis (ARN) is a serious ophthalmologic condition characterized by vitritis and occlusive vasculitis, which produce full thickness necrotizing retinitis (Fisher *et al*, 1982). ARN is commonly caused by Herpes viruses, usually varicella zoster virus (VZV) and herpes simplex virus (HSV).

Although human cytomegalovirus (HCMV) is a member of the Herpesviridae family, there are only few reports of ARN attributed to HCMV (Knox *et al*, 1998; Ganatra *et al*, 2000; Gargiulo *et al*, 2003). ARN can be readily diagnosed during routine, non-invasive ophthalmologic examination. However, the exact etiologic diagnosis of this sight-threatening eye condition is crucial in its management. Polymerase chain reaction (PCR)-based analysis of

vitreous aspirate plays a vital role in the diagnosis of such cases (Tran *et al*, 2003).

CASE REPORT

A 45-year-old Filipino consulted a physician because of blurring of vision associated with floaters in her left eye. She has a 15-year history of diabetes mellitus and underwent kidney transplant for renal failure in 1997. She has been maintained on low dose oral steroid and immunosuppressive agents for the past ten years. On initial consultation, her visual acuity was 20/70 in the right eye, improved to 20/30 on pinhole. The visual acuity in the left was 20/70, and not improved on pinhole. On slit lamp biomicroscopy, the right eye was normal but the left eye showed low-grade anterior segment inflammation associated with few retrolental cells and 2+ vitreous cells. Dilated funduscopic examinations revealed a normal right retina and optic nerve. The left eye showed a massive arterial occlusion nasally with sheathing of blood vessels. Areas of hemorrhage within a large area of necrotic

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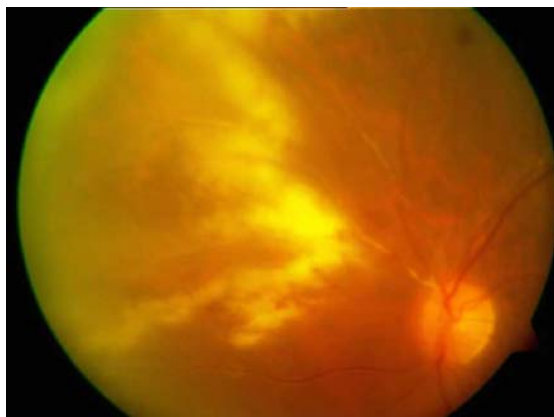


Fig 1—Acute retinal necrosis, left eye.

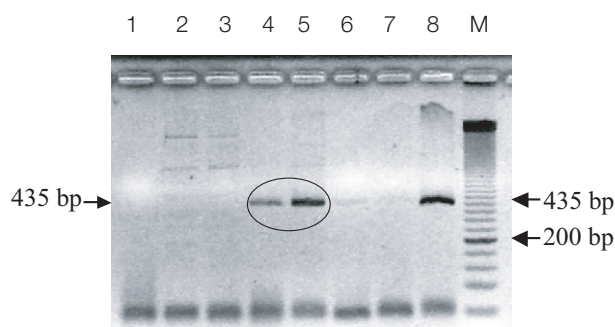


Fig 2—Detection of human CMV DNA by PCR Amplification. Lane 1: negative control (no band detected); lanes 2 and 3: patient sample in duplicate (not this case) negative for human CMV; lanes 4 and 5: patient sample in duplicate (this case) positive for human CMV (band at 435 bp); lanes 6 and 7: CMV AD 169 positive control (2 µl template); lane 8: CMV AD 169 positive control (3 µl template); M: 50 bp molecular weight marker. Expected amplicon size for human CMV was 435 bp.

retina with associated detachment were likewise noted (Fig 1). With the clinical picture and pertinent past medical history of the patient, the initial assessment was acute retinal necrosis, left eye.

Vitreous aspirate was analyzed for the presence of HCMV and HSV using PCR. The PCR results were positive for HCMV DNA

(band at 435 bp) and negative for HSV DNA (gel not shown). The diagnosis of HCMV retinitis was confirmed by a positive PCR on vitreous aspirate (Fig 2).

Based on the clinical findings and PCR results, the final diagnosis was ARN secondary to HCMV. The patient was then referred to both an infectious disease specialist as well as a nephrologist for co-management. Because of the nephrotoxic effects of intravenous ganciclovir treatment, the use of intravitreal injection was preferred in this case. The patient also underwent pan-retinal photocoagulation to prevent further detachment of the retina. The patient's vision initially improved to 20/50 two weeks post-injection but the patient was lost to follow-up.

DISCUSSION

Our findings demonstrate that the use of PCR-based assay for detecting herpes viruses in vitreous aspirate is helpful for the viral DNA detection of the etiologic agent. PCR-based analysis should include search for herpes viruses such as HCMV and HSV, as diagnostic dilemmas may prolong treatment of this sight-threatening disease. Knowing the etiologic agent of this sight threatening eye condition is crucial in its management.

Expected outcomes of ARN syndrome include progressive visual loss, retinal detachment in 50-75% cases within 3 months, final visual acuity <6/60 and visual prognosis may be poorer (Gartry *et al*, 1991). The diagnosis of acute retinal necrosis relies solely on clinical appearances. However, in atypical cases or in clinical uncertainty, PCR-based analysis of intraocular fluid should not be delayed. Most reported cases of ARN syndrome have been caused by VZV, accounting for 50-80% of cases, with HSV responsible for the remaining cases (Muthiah *et al*, 2007).

The primary consideration was acute retinal necrosis, most likely secondary to a viral

etiology (HCMV/HSV/VZV). Differential diagnosis included frosted branch angitis, HCMV retinitis, and multifocal hemorrhagic vasculitis. The presence of periarteritis rather than periphlebitis and its associated intra-retinal hemorrhage helps distinguish ARN from HCMV retinitis or acute multifocal retinitis. Moreover, prominent vitritis, retinal detachment and anterior uveitis separate ARN from HCMV retinitis. Patients with ARN often complain of pain related to episcleritis and floaters related to vitreous cellular infiltration. Complete blood count revealed leukocytosis. Chest x-ray was normal. HCMV IgG was positive while IgM was negative.

PCR-based assays of vitreous aspirate may provide a valuable tool in the diagnosis of patients with retinitis caused by herpes viruses. In general, the advantages of molecular-based diagnostics include the following: (i) it is intended for rapid diagnosis; (ii) minimal sample is required; (iii) it has a high analytical sensitivity and specificity; (iv) it may be useful for strain differentiation; (v) some viruses are difficult to cultivate or will take weeks to culture; and (vi) it provides more definitive diagnostic information (Fox *et al*, 1991; McCann *et al*, 1995; Nogueira *et al*, 2001). The development of multiplex PCR has allowed simultaneous screening for HCMV, HSV, VZV, and *Toxoplasma gondii* in a single reaction, without loss of specificity (Dabil *et al*, 2001). Real-time PCR has allowed the rapid quantitation of infectious posterior uveitis pathogens (Dworkin *et al*, 2002).

Acute retinal necrosis is a rare retinopathy and only a few cases are due to HCMV. PCR detection of HCMV in vitreous aspirate permits prompt diagnosis and treatment which are crucial to reduce visual loss.

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