Post-phacoemulsification cytomegalovirus corneal endotheliitis diagnosis and management

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Quantitative polymerase chain reaction is essential in diagnosing and monitoring cytomegalovirus endotheliitis. Treatment with long-term anti-virals and endothelial surgery can offer successful visual rehabilitation.

Case Report

A 68-year-old British-Chinese gentleman with left ocular hypertension was referred to the inflammatory eye diseases clinic with a presumed left keratouveitis that developed six weeks after uneventful phacoemulsification surgery with intraocular lens implantation. This had failed to resolve with oc. aciclovir 3% and intensive g. dexamethasone 0.1%. His left vision was 20/60, associated with dense corneal stromal edema (Figure 1a), keratic precipitates (KPs) (Figure 1b), mild anterior chamber inflammation, and an intraocular pressure (IOP) of 23 mmHg. The posterior segment appeared healthy with no evidence of vitritis, choroiditis or retinitis, and a normal optic disc.

An infectious etiology was suspected and a diagnostic multiplex quantitative polymerase chain reaction (qPCR) analysis of an aqueous humor (AqH) sample taken at the slit-lamp confirmed left corneal endotheliitis secondary to cytomegalovirus (CMV) (CMV, 150,000 DNA copies/ml; Epstein-Barr virus [EBV], weakly positive; and negative for herpes simplex virus, varicella zoster virus, fungal 18S-rRNA, and bacterial-16S rRNA). EBV DNA was also detected in whole blood. The patient was commenced on oral valganciclovir 900 mg b.i.d. for 21 days followed by 450 mg b.i.d. and non-preserved g. dexamethasone 0.1% qid for three months.

Initial improvement in his clinical condition was supported by repeat whole blood and AqH qPCR detecting only EBV DNA (whole-blood 3,700 copies/ml, AqH 17,600 copies/ml). Although 95% of adults worldwide are believed to have serological evidence of EBV infection, intraocular EBV is strongly associated with central nervous system lymphoma in AIDS.1 A haematological opinion was thus sought and excluded systemic lymphoma.

Interruption of valganciclovir treatment (due to non-availability in the community), resulted in an acute re-presentation with a severely painful left eye and reduced vision of hand movements at 30 cm. Examination revealed inferior haemorrhagic anterior scleritis (Figure 1c), a bullous keratopathy, and inferior KPs consistent with a diagnosis of recurrent CMV endotheliitis and associated scleritis, confirmed by qPCR of the AqH detecting CMV DNA (1800 copies/ml). IOP was 28 mmHg and fundal examination was normal. The patient was commenced on intravenous ganciclovir 500 mg once daily for 14 days switching to oral valganciclovir 900 mg b.i.d. for 21 days followed by a maintenance dose of 900 mg once daily, flurbiprofen 100 mg thrice daily for one month and intensive non-preserved g.dexamethasone 0.1%. Within one week there were significant improvements in the endotheliitis and scleritis, and by four weeks, only mild corneal decompensation and endothelial pigmentation remained (ventral aortic 20/30).

Oral valganciclovir was discontinued after six months following a negative AqH qPCR for CMV DNA. Nevertheless, after continued progression of corneal endothelial dysfunction (endothelial
cell count of 386/mm²) and concomitant declining visual acuity (6/200), the patient underwent an 8 mm Descemet’s stripping automated endothelial keratoplasty with concurrent implementation of strict perioperative management strategies summarized in Figure 2. An intraoperative AqH sample and the stripped endothelium were negative for CMV, EBV, herpes simplex virus, varicella zoster virus DNA. Four weeks postoperatively, vision improved to 20/30, the corneal edema had resolved (Figure 1d) and IOP was maintained at 14 mmHg. By seven months follow up, all topical and systemic therapy had been discontinued, and the cornea remained clear without further relapses of endotheliitis.

**Discussion**

CMV is a β-herpesvirus detected in the serum of 45%–100% of the population worldwide. Primary infection is usually asymptomatic in the immunocompetent but can have serious implications for immunocompromised hosts. Innate immune mechanisms are important for first-line defense, but the virus demonstrates latency through an adaptive T-cell response involving primarily effector memory cytotoxic CD8+ T-cells. Breaches of the normal immunoprotective ocular microenvironment e.g. through surgical trauma results in activation of disease. Ocular involvement in the form of endotheliitis, anterior uveitis, Fuch’s heterochromic iridocyclitis and Posner-Schlossman syndrome are recognized entities. CMV endotheliitis is rare with all currently documented cases restricted geographically to the Asia-Pacific where CMV is prevalent amongst the population.

CMV endotheliitis may present as a primary endotheliitis or in conjunction with a recurrent anterior uveitis. It has frequently been reported following ocular surgery including Descemet’s stripping automated endothelial keratoplasty. Endotheliitis is characterized by the presence of KPs, Descemet’s membrane folds and corneal oedema configured in a disciform or sectoral pattern, often accompanied by a mild anterior uveitis and/or ocular hypertension. It can also present as corneal oedema and Descemet’s membrane folds in the absence of KPs. The differential diagnoses include postoperative corneal decompensation, acutely raised IOP (trabeculitis, Posner-Schlossman syndrome), or inflammation (due to retained soft lens matter), herpes simplex virus/varicella zoster virus keratouveitis or Fuch’s heterochromic iridocyclitis).

CMV endotheliitis was first described in 2006 in a Japanese patient who had CMV DNA detected in the AqH. Distinctive owl’s eye morphological cellular changes typical of CMV were subsequently identified in vivo using corneal endothelial confocal microscopy in another affected patient. The detection of CMV DNA in the AqH is vital for assisting the diagnosis, and has particular implications for therapeutic intervention. CMV responds poorly to systemic and topical aciclovir (as exemplified by our patient), but can be treated successfully with oral valganciclovir, or with intravenous and topical ganciclovir. Recent studies utilizing qPCR have demonstrated a significant relationship between AqH CMV load and rate of endothelial cell loss. Treatment with antiviral therapy also results in a decreased AqH viral load. Serial AqH sampling, therefore, represents a useful tool for quantifying the severity.
Evidence-based therapeutic algorithm to manage acute manifestations and relapses with or without associated scleritis and sclerokeratitis is illustrated. Implementation of a strict perioperative regime is recommended for any planned intraocular surgical procedure to optimize visual outcome and minimize the risk of surgically induced CMV endotheliitis and sclerokeratitis. Confirmatory qPCR of AqH should be performed, and if corneal transplant surgery is undertaken, excised host endothelium or penetrating keratoplasty tissue should be analysed by qPCR, histopathology and immunofluorescence studies for evidence of active CMV infection i.e. characteristic ‘owl’s eyes’.

(AqH, aqueous humour; qPCR, quantitative PCR; CMV, cytomegalovirus;)

| Acute Manifestation | Relapse with Scleritis or Sclerokeratitis |
|---------------------|----------------------------------------|
| Oral valganciclovir 900mg bid for 21 days followed by 450mg bid for three months (or until AqH CMV cDNA negative) | Intravenous ganciclovir 500mg od for 14 days, switching to oral valganciclovir 900mg bid for a further 21 days, and maintenance dose of 900mg od for six months (or until AqH CMV cDNA negative) |
| Non-preserved g. dexamethasone 0.1% qid for three months | Flurbiprofen 100mg tid for one month ± iv methylprednisolone 1g with supplementary ‘post-pulse’ oral prednisone/ prednisolone if not responding to NSAIDs |
| Contemplation of Surgery | Non-preserved g. dexamethasone 0.1% 2 hourly |
| Negative AqH qPCR for CMV cDNA | Inflammation free for three months |
| Preoperative Conditioning (Two weeks) | Perioperative Period |
| Oral valganciclovir 900mg bid | Three pulses of iv methylprednisolone 1g on the day of surgery and for two further consecutive days |
| Non-preserved g. dexamethasone 0.1% 2 hourly | Intraoperative investigations include |
| | AqH |
| | qPCR |
| | Excised host endothelium |
| | qPCR |
| | Histopathology/ Immunofluorescence analyses |
| Postoperative Period | Oral valganciclovir 900mg bid for two followed by a maintenance dose of 900mg od for 5-6 months |
| | Non-preserved g. dexamethasone 0.1% 2 hourly for two weeks after surgery then qid for a minimum of 5-6 months |
of the disease and for monitoring response to therapy not only for CMV endotheliitis, but also for CMV associated scleritis.

Our patient developed severe endotheliitis and represents the first reported case of secondary haemorrhagic scleritis following abrupt cessation of valganciclovir. This was highly responsive to intravenous ganciclovir, oral flurbiprofen and intensive topical glucocorticoids, followed by maintenance on oral valganciclovir obtaining complete remission, but with secondary, clinically significant, irreversible corneal endothelial dysfunction. This was treated successfully with small-incision, selective endothelial corneal transplant surgery accompanied by a strict evidence-based protocol to minimize surgically-induced exacerbations/recurrence of disease (Figure 2).

CMV endotheliitis can be a difficult condition to treat and is often triggered by intraocular surgery. We have suggested a treatment algorithm that can be followed for resistant cases or if further intraocular surgery is contemplated.

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