

# Cytomegalovirus-related corneal endotheliitis A review article



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## Abstract

Cytomegalovirus (CMV)-related corneal endotheliitis is an inflammation of the corneal endothelium caused by CMV. It typically presents as coin-shaped keratic precipitates (KPs), with or without corneal edema, in otherwise healthy individuals. It may be associated with anterior uveitis and raised intraocular pressure (IOP). Patients with CMV-related corneal endotheliitis respond to systemic and topical ganciclovir with the use of topical steroid. Making an accurate early diagnosis is crucial in preventing loss of corneal endothelial cells and unnecessary treatment resulting from misdiagnosis in these patients.

**Keywords:** Endotheliitis, Corneal endothelium, Cytomegalovirus, Ganciclovir

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## Introduction

Corneal endotheliitis, an inflammation of the corneal endothelium, is characterized by corneal edema, keratic precipitates (KPs), and mild to moderate anterior chamber inflammation. This clinical entity can be attributed to various causes, all of which share a common site of inflammation—corneal endothelial cells. Hence, inflammatory entities (e.g., epithelial keratitis and interstitial keratitis) that involve other parts of the cornea—namely, the epithelium and the stroma—do not fit the criterion of this disease. Corneal endotheliitis is caused by a variety of mechanisms, including immune-related mechanisms without any known causative organisms (e.g., graft rejection following penetrating keratoplasty) and infectious mechanisms, such as those caused by viruses. Research has shown that corneal endotheliitis can be caused by herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV)<sup>19</sup>, and mumps infection<sup>23</sup>.

Human CMV, a ubiquitous lymphotropic herpes virus, causes various systemic and ocular clinical entities, including retinitis in immunocompromised hosts. Ocular CMV manifestations range from corneal endotheliitis, episodic anterior

uveitis, sector iris atrophy with iritis, chronic anterior uveitis, and, ultimately, to retinitis. A few cases of CMV-related corneal stromal<sup>13,28</sup> and endothelial changes<sup>10,20</sup> have been reported in immunocompromised patients. Recent research has shown an increasing number of cases of CMV-associated anterior segment inflammation with a different range of clinical presentations (including anterior uveitis, corneal endotheliitis, or both) in otherwise healthy individuals<sup>6,7,16,17,18,25,27</sup>. This is a review article that discusses the pathology, diagnosis, and management of CMV-related endotheliitis.

## Pathophysiology

The exact mechanism of corneal endotheliitis is not yet clear. Research initially suggested that the mechanism of corneal endotheliitis was autoimmune related, based on its similarity with graft rejection and good response to topical corticosteroid treatment<sup>15</sup>. However, with advances in diagnostic procedures, more recent research has indicated that this clinical entity may be caused by viruses like CMV. One possible explanation is that corneal endotheliitis is an autoim-

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immune entity that is triggered by microorganisms like viruses. Suzuki and Ohashi<sup>24</sup> proposed that corneal endotheliitis is an anterior chamber-associated immune deviation (ACAID)-related disease. They posited that a varied dose of virus is shed into the anterior chamber whenever the virus that has established a latent infection becomes intermittently reactivated. Repeated shedding of virus particles leads to the induction of ACAID against viral antigens. Infection occurs when the preexisting antibodies are incapable of neutralizing the reactivated virus. This mechanism could explain why some patients respond to topical anti-inflammatory treatment but experience a relapse or recurrence after stopping the treatment. By contrast, if the treatment regimen includes anti-virus medication, patients with CMV-related corneal endotheliitis respond nicely.

Research has shown that murine CMV in immunocompetent mice causes a transient, self-limited infection mainly in the anterior segment, with only minimal involvement of the posterior segment<sup>2</sup>. This finding could explain why most CMV-related corneal endotheliitis and uveitis cases occur in immunocompetent patients. The range of ocular manifestations of CMV and the variation between immunocompetent and immune-deficient patients may depend on the ocular immune response and/or the viral load. Hence, the anterior segment entities being the main mode of expression of infection in relatively competent immune systems and posterior segment involvement in immunocompromised subjects<sup>4</sup>.

## Clinical features

The clinical features of corneal endotheliitis consist of KPs and a corneal edema without the involvement of the other corneal layers. Typically, CMV-related corneal endotheliitis occurs in immunocompetent patients who are not afflicted with any other diseases. Inflammation of the corneal endothelium may or may not be associated with anterior uveitis<sup>7,18</sup>. High intraocular pressure (IOP) can occur in patients with CMV-related corneal endotheliitis; its occurrence may be related to inflammation of the trabecular meshwork. Koizumi et al.<sup>17</sup> found that 7 of 8 (87%) of their patients with high IOP responded nicely after treatment specific for CMV. In addition, CMV-related corneal endotheliitis can mimic other clinical entities. In some patients, it may present as chronic anterior uveitis and recurrent episodic iritis with raised IOP, resembling Posner-Schlossman syndrome (PSS), and in others, it may present with anterior chamber cells and endothelial KPs, resembling Fuchs' heterochromic iridocyclitis (FHI)<sup>7</sup>.

Based on the distribution of the KPs and configuration of the overlying stromal and epithelial edema, corneal endotheliitis can be classified into four forms: linear, sectorial, disciform, and diffuse. In both the linear and sectorial forms, the corneal edema is localized; however, the distribution of KPs differs—that is, it is linear in the former but is disseminated to involve the area of the edema in the latter form. In disciform corneal endotheliitis, a round or disc-shaped stromal edema is present in the central or paracentral region of the cornea, and numerous KPs form inside the corneal edema. In diffuse corneal endotheliitis, the edema is spread over the entire cornea and fine KPs are scattered within the lesion. CMV-related corneal endotheliitis rarely presents in the diffuse form.

## Diagnosis

In general, corneal endotheliitis is a clinical diagnosis. Corneal endotheliitis associated with specific coin-shaped KPs could be used as a screening tool for CMV-related anterior segment infection, especially if it is associated with high IOP and corticosteroid-recalcitrant inflammation<sup>12</sup>. In cases of CMV-related corneal endotheliitis, isolation of the virus from the anterior chamber is necessary before starting the required treatment. Because the aqueous humor is generally free from any pathogens, a positive result obtained by polymerase chain reaction (PCR) should be considered reliable provided that contamination from the technique itself is excluded<sup>14</sup>. Anterior chamber fluid can be tested for the presence of viral DNA and local antibody production. A combination of these tests is preferred because test results can vary during the course of the disease<sup>21</sup>. Testing for DNA tends to be positive at the onset (and/or early at reactivation), and antibody testing can be positive at any point in time. In general, the aqueous humor should be analyzed by PCR for HSV, VZV, and CMV DNA<sup>21</sup>.

The Goldmann-Witmer coefficient (GWC) can also be calculated for aqueous fluid so as to exclude the possibility of passive diffusion from the patient serum. The GWC is defined as titer of antibody in aqueous/titer of antibody in serum X total serum globulins: total aqueous globulins<sup>11,21</sup>. A GWC can be considered positive (i.e., suggestive of intraocular antibody production) when the value exceeds 3. Detection of corneal endothelial pathology (e.g., pseudoguttata or owl's eye) can sometimes be performed with *in vivo* confocal microscopy<sup>22</sup>.

## Treatment

The treatment of CMV-related corneal endotheliitis should target both its infectious and inflammatory components. One rational strategy is appropriate systemic and antiviral treatment with topical corticosteroids. Most current treatment regimens are drawn from knowledge of CMV-related retinitis in immunocompromised patients. Ganciclovir, a potent antiviral medication used to treat or prevent CMV infections and other members of the herpes virus family, has been widely used in its systemic form to treat CMV-related retinitis. By inhibiting viral DNA polymerase, ganciclovir terminates the elongation of viral DNA, which in turn arrests viral replication. Topical ganciclovir 0.15% gel has also been shown to be effective in the treatment of active herpetic epithelial keratitis<sup>8</sup>, in the prophylaxis against herpetic keratitis following keratoplasty<sup>26</sup>, and in the treatment of CMV-related uveitis<sup>5</sup>. Corneal penetration of topical ganciclovir is good and can reach therapeutic levels in the aqueous humor<sup>3,9</sup>. Ganciclovir given in gel form is easy to apply and seems to be a safe alternative to the more toxic systemic form.

When Koizumi et al.<sup>17</sup> used systemic ganciclovir to treat 8 patients with CMV-induced corneal endotheliitis, all patients exhibited a quick clinical response to the treatment. In their study, 7 patients received IV ganciclovir (5–10 mg/kg), and 1 patient received oral form valacyclovir (1500 mg/day). All patients received topical corticosteroids; 4 patients received 0.3% topical acyclovir, 3–5 times per day, and the other 4 patients received 0.5% topical ganciclovir, 6–8 times per day. In another study, Anshu et al.<sup>1</sup> treated 4 patients who had been

diagnosed with CMV-related endotheliitis following Descemet's stripping automated endothelial keratoplasty (DSAEK) with oral valganciclovir 900 mg twice daily for 6 weeks, followed by 900 mg once daily for a further 6 weeks. Patients also received topical steroids, topical antiglaucoma medications, and topical ganciclovir as needed. All patients responded to treatment and grafts remained clear in 3 of the 4 patients. After completion of treatment, 2 patients had recurrence of inflammation, with mean time to recurrence of 8 months. Thus, CMV-related corneal endotheliitis responds nicely to ganciclovir but can recur after discontinuation of the treatment.

Physicians should inform patients about the potential for hematologic toxicity secondary to systemic administration of ganciclovir and, consequently, monitor patients periodically. If myelosuppression or pancytopenia occurs, the treatment should be discontinued.

## Conclusions

CMV-related corneal endotheliitis is manifested by corneal edema in various locations, the presence of KPs, and a mild anterior chamber reaction, and is usually associated with raised IOP. Misdiagnoses and delays in treatment may occur because CMV-related cornea endotheliitis can mimic other clinical diagnoses. Further study is needed to investigate other aspects of the disease, such as pathogenesis, ways of prevention, and efficient treatment modalities.

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