Cytomegalovirus Detection After Penetrating Keratoplasty

Abstract

Cytomegalovirus is an opportunistic large-enveloped pathogen of the herpesvirus family, inducing several ocular diseases, both retinal and corneal infections. CMV has been mostly found in eyes with failed cornea grafts and has been described with keratic precipitates and stromal edema. In this study, we describe the outcomes of a CMV infection diagnosis following a perforating keratoplasty.

This study is a prospective case report. CMV was found in the stroma of a patient's cornea transplant on her second penetrating keratoplasty. Therefore, the patient received 0.15% valganciclovir gel 1.5mg. The follow-up was made clinically and by confocal microscopy. After corneal ulceration, topical ganciclovir was stopped and no other drugs were introduced. CMV endotheliitis may possibly be activated by the intensive immunosuppressive therapy received by our patient after two grafts and should be added to the list of etiologic of stromal edema after perforating keratoplasty.

Keywords: Cytomegalovirus; Penetrating keratoplasty; Ganciclovir; Polymerase chain reaction; Owl's eye

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpesvirus family, inducing a possibility of retinal and corneal infections [1]. The first report of CMV induced corneal endotheliitis was described in 2006 on a patient with unilateral corneal oedema without any immunodeficiency and found by polymerase chain reaction (PCR) in aqueous humor [2]. Few publications existed and described the corneal lesions associated with this infection. The corneal endotheliitis presentation is normally a corneal endothelial cell loss, local stromal oedema and keratic precipitates (KP), sometimes iris atrophy or high intraocular pressure. There is a relation between the CMV viral load in aqueous humor and the endothelial cell loss [1]. In the last ten years, the involvement of CMV has been increasingly recognized in the anterior segment disease. This virus is a new etiologic agent for corneal endotheliitis. Cytomegalovirus corneal endotheliitis may represent a newly identified clinical entity of corneal oedema. CMV has been mostly found in eyes with failed cornea grafts. Corneal endotheliitis might mimic allograft rejection after perforating keratoplasty (PKP). In some reports, the development of CMV endotheliitis was preceded by corticosteroid treatment or penetrating corneal surgery. There is no protocol for the treatment of these eyes. Untreated, CMV endotheliitis can lead to corneal decompensation, whereas specific treatment can lead to a decrease of the oedema avoiding the need for transplantation [3]. Each ophthalmological team around the world chose a topical or systemic treatment based on ganciclovir which is converted into ganciclovir triphosphate who inhibits the viral DNA polymerase and stops the CMV replication. In water, the pH of ganciclovir is between 9 and 11. In this study, we describe a corneal CMV infection after PKP. Since there are no guidelines for the dosage of the topical treatment, we decided to evaluate the pH for some dosage described in the literature.

Case Report

A 42-year-old woman had a history of congenital aniridia and severe glaucoma in both eyes. Right eye underwent evisceration in 1986 after traumatism. Since 2005, a first perforating keratoplasty (PKP) was performed on the left eye because of an intraocular pressure elevation followed by a development of a corneal decompensation requiring transplantation. She received Tobradex (Alcon, USA) with a gradually reduced dosage. A second PKP was performed for corneal ulcer without any healing process. A failed cornea graft appeared in 2016. The patient received treatment with local corticosteroid eye drops successively on the long term and finally cyclosporine...
CMV was found in the stroma of the second corneal graft. The epithelium is slightly thinner in some zone. There is some fibrotic pannus under epithelial cells. Enlarged cells were seen in the corneal stroma (cytomegaly) with prominent nuclear inclusion, which consisted in a large central inclusion surrounded by a clear halo, giving an “owl’s eye” appearance, specific for CMV. There is no neovascularization inside the cornea. The histological staining was positive for CMV only in the stroma and not in the endothelium (Figure 1). The PCR from herpes simplex virus and varicella-zoster virus returned negatives. The PCR CMV returned positive.

Discussion

The diagnosis of CMV for our patient was unexpected since she had no KP and no history of any viral infection. In the literature, KP is described as a coin-shaped pattern resembling a virus-induced plaque in cell culture. Koizumi et al. [2] thought coin-shaped KPs were a characteristic sign of CMV endotheliitis. CMV endotheliitis may have possibly be activated by the intensive immunosuppressive therapy received by our patient after two grafts. Virus reactivation is normally controlled by the immune system, but with long-term corticosteroid treatment, the immune system has been compromised.

The anterior chamber is an immune-privileged site and might be an optimal site for CMV to reactivate. Most of the diagnosis in the few articles have been made by anterior chamber tapping. In our study, the diagnosis was made only by the anatomopathological analysis. We didn’t perform any anterior chamber tapping knowing the risk for the patient since the patient was a one-eyed young woman, with a history of three PKP, congenital aniridia, and post-operative choroidal detachment. We used the slit-lamp examination and confocal microscopy for the efficacy of follow-up.

This study is, to our knowledge, the first to describe stromal CMV infection diagnosed by an anatomopathological analysis. Owl’s eye morphology is formed by a large, intranuclear inclusion body and is frequently seen in the pathologic specimens obtained during autopsy and biopsy. This is a sure sign finding of CMV infection [4]. Confocal microscopy could help for the diagnosis and follow-up whereas biopsy of the corneal endothelial doesn’t exist. The possibility to send to the laboratory, for each PKP done, some anterior chamber liquid could be another solution.

CMV after PKP is a completely new aetiology of stromal oedema. 7 from 11 eyes presenting corneal stroma oedema and KP after PKP were positive for CMV in the study of Chee. Each patient with these lesions was referred for an aqueous tap [5]. Prophylactic treatment with perioperative ganciclovir might improve the outcomes of repeat corneal transplants in these types of eyes. Some treatment existed now, systemic or topical.

Long-term therapy is recommended to prevent recurrence especially after receiving corneal transplant [1,6]. The potential side-effects associated with systemic ganciclovir render it’s inaccessible for clinical practice and administration of oral ganciclovir leads to low drug concentration at the cornea infected eye [7]. An optimum treatment must be considered for effective management of this corneal disease. Thus, treatment for corneal endotheliitis uses a local treatment. Less than 5-10% of the drug that overcomes the precorneal clearance mechanisms enters the eye. Two publications exist about CMV endotheliitis following PKP. Our study discusses treatment for CMV found in the stroma of the cornea graft. It means that the patient has possibly CMV in the rim of the cornea. Preparations of 0.3% acyclovir ointment, 0.15-0.5% ganciclovir drop, 0.5% valganciclovir gel and 2% ganciclovir have

The patient has a dear corneal graft, with no sign of inflammation in the anterior chamber, no KP and without any oedema. The confocal microscopy performed didn’t show any sign of stromal inflamed keratocytes or endotheliitis. No oral drugs were prescribed because of the lack of evidence in the literature in these types of cases. A close follow-up was done every week.

Since the management of this infection was not well described in the literature, and the patient didn’t have any sign of inflammation, we decided to test the pH of dosage of topical ganciclovir drops already known in other studies. The pharmaceutical laboratory already tested preparations from 0.75 to 2.0% ganciclovir drop were tested by our pharmaceutical laboratory. All these tests came back with a pH bigger than 10, toxic for the cornea. The pH for the 0.15% valganciclovir gel has not been tested because already in the back with a pH bigger than 10, toxic for the cornea. The pH for the already known in other studies. The pharmaceutical laboratory decided to test the pH of dosage of topical ganciclovir drops already in the literature, and the patient didn’t have any sign of inflammation, which consisted in a large central inclusion surrounded by a clear halo, giving an “owl’s eye” appearance, specific for CMV. There is no neovascularization inside the cornea. The histological staining was positive for CMV only in the stroma and not in the endothelium (Figure 1). The PCR from herpes simplex virus and varicella-zoster virus returned negatives. The PCR CMV returned positive.

![Figure 1: Anatomopathological analysis and histological staining of the second PKP. A and B: Corneal of the second graft of the patient.](https://peernest.org/ebooks.php)

---

The patient received 0.15% valganciclovir gel 1.5mg/g after surgery. But we needed to stop the local treatment because of the appearance of a corneal ulcer without healing, resolved after stopping treatment. We didn’t give any general or other local anti-CMV drugs because of the absence of inflammation clinically and on the confocal microscopy.
been reported as topical maintenance therapies for the long-term prevention of CMV endotheliitis in recent publications [6,8,9]. Nakagawa evaluated the cytotoxicity of 2.0% ganciclovir eye drops using cultured rabbit corneal cells in vitro [10]. This drop did not demonstrate any cell cytotoxicity for cultured corneal cells after 5 minutes, this finding suggested that it could be used in a clinical setting. Intracameral ganciclovir injection has been suggested but Choi et al. found ganciclovir had a cytotoxicity effect on cultural human corneal endothelial cells with this kind of treatment if the concentration is >5mg/mL [11]. It could be an effective treatment with the right concentration for CMV endotheliitis.

However, the toxicity of the drops is a real matter for these patients with delicate cornea and graft failure history. This study is the first to test the pH of the ganciclovir drop in a pharmaceutical laboratory. With 2% ganciclovir, the pH was 11, hence highly toxic for the cornea. Ophthalmic pharmaceuticals have to be extraordinarily pure and free from physical, chemical, biological contaminants and suitably compounded and packaged for instillation into the eye. Normal tears have a pH of 7.4 and possess some buffering effect. The range of 4-8 pH is tolerated by a normal eye. The final pH of the solution is often a compromise between isotonicity, stability, precipitation. Preservatives should not be added because the cornea transplants are sensitive to these substances [12,13]. Unfortunately, in our laboratory, with several essays of different percentages of dilution, all drops were toxic for the cornea. We didn’t find any solution to treat our patient.

Conclusion

CMV should be added to the list of etiologic pathogens causing corneal endotheliitis and also an etiologic of stromal oedema after PKP. Further studies and laboratory analysis need to be done to find a possible local treatment in case of preventive care.

References