A case of herpesviral corneal endotheliitis presenting with corneal endothelial defect

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Dear Editor,

Corneal endotheliitis, first reported in 1982 as an autoimmune disorder by Khodadoust and Attarzadeh[1], is now recognized to be frequently induced by viral infections, including varicella zoster virus (VZV), cytomegalovirus (CMV) and herpes simplex virus (HSV), that can cause inflammatory and immune-related injuries or direct damages to corneal endothelial cells[2-3]. In cases with this type of endotheliitis of viral origin, manifestations may include conjunctival ciliary congestion or mixed congestion, corneal subepithelial bulla, localized corneal edema, keratic precipitates (KP) characteristic to the edema area, puckered posterior elastic lamina, mild anterior chamber reaction, intraocular pressure (IOP) elevation in presence of inflammation in trabecular meshwork, and endothelial decompensation[3-4]. Accurate diagnosis of viral corneal endotheliitis is challenging due to its complex presentation, leading to a high misdiagnosis rate. To the best of our knowledge, there was no previous report of viral corneal endotheliitis presenting with corneal endothelial defects in the English literature. Here, we report a case of herpesviral corneal endotheliitis presenting with corneal endothelial defect and bullous keratopathy, in an attempt to advance our understanding and management of this condition. This case adhered to the Declaration of Helsinki and gained approval from Zhujiang Hospital’s Research Ethics Committee of Southern Medical University (No.2022-KY-199). The informed consent was obtained from the subject.

CASE PRESENTATION

A 55-year-old male admitted to our hospital due to one month of experiencing foreign body sensation, redness, and pain in the right eye. Hence, he sought medical attention at our hospital and was diagnosed with herpes zoster viral eyelid dermatitis in the right eye, with an IOP measured 17 mm Hg. Then he received systemic and topical antiviral, analgesic and nutritional neurotherapy. Two days later, he returned with an IOP measured 59 mm Hg, diagnosed with VZV-infected keratitis and secondary glaucoma. Despite robust immunity, he reported a VZV infection on the right frontoparietal region and eyelid skin 1mo prior to eye symptoms. The patient did not comply with hospital admission and was advised to use multiple eye drops, including gatifloxacin eye-drop, acyclovir eye-drop, recombinant bovine basic fibroblast growth factor (rb-bFGF) eye-gel, and timolol eye-drop. Despite this, symptoms persisted, prompting his return to our hospital, where a lesion in the corneal endothelium was observed. Admission examination revealed that the best corrected visual acuity (BCVA) and IOP were 0.2 (decimal) and 19 mm Hg in the right eye and 1.0 and 17 mm Hg in the left eye, respectively. Slit-lamp microscopy: mild congestion in the right eyelid margin; pitting scars due to a scab that fell off from the right frontoparietal region and the eyelid skin, which did not cross over the midline of the face (Figure 1A); mixed conjunctival congestion (+) and edema (+++); cystic changes and stromal edema in the middle and temporal-side of the corneal epithelium, with dense, diffuse and punctate pigmented defects; neovascularization in the stromal layer at the 7–9-o’clock position; a circular defect sized 1 mm×1 mm in the corneal endothelium proximal to the pupils at the 9-o’clock position; absence of KP; normal anterior chamber depth with clear aqueous humor but sort of mild opacities in the lens (Figure 1B, 1C). Corneal perception was tested using a cotton swab, showing diminished perception in the right eye while normal perception...
in the left eye. Anterior segment optical coherence tomography (AS-OCT) demonstrated partial endothelial defect and the central corneal thickness of 839 μm in the right eye (Figure 1D). Specular microscopy showed that the corneal endothelial density in the right eye was not calculable due to edema while the left eye was had a density of 2793.4 cells/mm² with 56% hexagons cells. Hematological and rheumatologic investigations were unremarkable. The patient, presumed to have VZV corneal endotheliitis, received treatment with systemic acyclovir injections [250 mg, intravenous injection (I.V.), 8h per time] and topical acyclovir eye-drop (6 drops daily), levofloxacin eye-drop (4 drops daily), recombinant human epidermal growth factor eye-drop (4 drops daily), rb-bFGF eye-gel (2 times daily). However, on day 3 of the treatment, the BCVA and IOP in the right eye were 0.06 and 24.6 mm Hg, and there was disease progression with an enlargement of the corneal endothelial defect which enlarged to 2 mm×1.5 mm (Figure 2A, 2B). Considering inadequate clinical response to anti-viral treatment and disease progression, acyclovir was discontinued and replaced by ganciclovir as the follow, ganciclovir injections (250 mg, I.V., 12h per time), 0.1% ganciclovir eye-drop (8 drops daily), 0.15% ganciclovir eye-gel (3 times daily). Renal function and blood routine examinations were performed during treatment. On day 5 of the treatment, there was no aggravation of the endothelial defect. Dexamethasone eye-drop and hypertonic saline eye-drop (both 4 drops daily) were provided, with a bandage contact lens. On day 6, the corneal endothelial defect was repaired. On day 11, the patient was allowed to discharge with the BCVA and IOP in the right eye of 0.6 and 13.6 mm Hg. There were reductions in the cystic changes in the corneal epithelium and the punctate staining range. In the meantime, the corneal stromal edema was alleviated and the endothelial defect was repaired. There was no KP and the aqueous humor was clear (Figure 2C, 2D). During the 3-month follow-up, the BCVA in the right eye was 0.8, without evidence of recurrence. The workflow for the case report is illustrated in Figure 3.

**DISCUSSION**

Viral corneal endotheliitis is believed to occur as a result of direct viral attack on the corneal endothelium and virus-induced delayed-type hypersensitivity. In the English literature, there are no case reports of a similar nature discussing viral corneal endotheliitis manifested as a corneal endothelial defect. It has been studied that corneal endothelial defect can lead to stromal edema and formation of epithelial and subepithelial bullae. Chiang et al. and Papaioannou et al. described the atypical clinical manifestations of viral corneal endotheliitis caused by HSV and CMV infections respectively, and reported absence of KP and increase of anterior chamber inflammatory reaction or IOP in patients with bullous corneal
CMV-infected cells, providing compelling evidence for this mechanism of injury[3,9]. Recent years saw AS-OCT crucial in ophthalmology, offering high-resolution anterior segment images for subclinical examination. Our case uniquely includes AS-OCT images of herpesviral corneal endotheliitis, vividly illustrating corneal endothelial defect. AS-OCT provides robust evidence, especially when corneal edema significantly impacts specular microscopy. In addition, the patient’s IOP ranged from 13 to 25 mm Hg during the treatment but peaked at 59 mm Hg before hospital admission, considering the viral attack on trabecular meshwork. There have been a variety of categories of viral corneal endotheliitis both domestically and abroad. A unified classification system at present is on the basis of KP distribution, which predominantly fall into three types: disciform, diffuse and linear[4]. In the present case, no typical KP was presented and there was no abnormality in the contralateral eye, ruling out Fuchs endothelial corneal dystrophy. Given the excellent therapeutic efficacy after anti-viral treatment and glucocorticoids administration, VZV-realted endotheliitis was strongly suspected. We also noted that the patient had an inadequate clinical response to acyclovir but responded better to ganciclovir given that there was no enlargement of the corneal endothelial defect after 2d of ganciclovir treatment. It demonstrated that ganciclovir eye-gel at 0.15% could be effective in treatment of the cornea and the anterior chamber with decreased viral copy numbers in the aqueous humor and reduced damages to the endothelial cells[9]. Kasetsuwan et al[10] first reported a case who had normal immune function but suffered corneal endotheliitis due to HSV and CMV infections. Al Somali et al[11] discovered a case of corneal endotheliitis caused by infections with both VZV and CMV. Both of the two cases poorly responded to acyclovir in early stages. Despite the CMV-related endotheliitis is readily to be mis-diagnosed as herpetic eye disease, CMV infection alone or in combination with VZV infection should be considered as well[12]. It is well believed that the in vivo repair of adult corneal endothelial cells is realized primarily by cell migration to the defect area rather than cell division activity. The present patient was treated with topical glucocorticoids and endothelial defect was repaired on the next day, suggesting that hormone administration is conducive to advancing migration of endothelial cells. At present, the efficacy of topical hormone administration is still on debate, as there is a risk of viral reactivation because of its suppressive effect on the cell-mediated immune response[13]. In this context, the timing, dose, and frequency of hormone applications should be determined based on the individual medical conditions. Basically, it is recommended to use hormones in cases with sufficient clinical response to anti-viral treatment, which can help for disease control and reduction of corneal endothelial injury. In the meantime, maintenance therapy is required upon control of inflammatory reactions[14]. In conclusion, corneal endothelial defect can be a clinical manifestation of atypical viral endotheliitis. If acyclovir treatment is ineffective, dual viruses instead of a single herpesvirus should be considered and diagnosed through aqueous analysis, confocal microscopy and AS-OCT. Additionally, early appropriate treatment is crucial to prevent permanent injury to the corneal endothelium. Topical hormone applications while sufficient clinical response to anti-viral treatment can help control disease progression by advancing the repair of endothelial defect.

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Herpesviral corneal endotheliitis

REFERENCES


