Herpes Simplex Epithelial Keratitis and Contact Lenses: A Case Report

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Abstract

Herpes simplex virus keratitis is an ocular infection arising from the reactivation of herpes simplex virus (HSV). If not promptly addressed, it can lead to diminished visual acuity and potential blindness in the affected eye. The sight-threatening aspects of this infection are primarily associated with the development of scarring and opacity. A 22-year-old woman, who was an otherwise healthy contact lens wearer, sought medical attention with complaints of painful, red, and photophobic eyes. Upon examination, a dendritic ulcer was observed on the right eye, accompanied by toxic keratopathy in both eyes. This was due to the fact that she used a spectacle lens cleaning solution to store her lenses before wearing them. The treatment regimen that was implemented consisted of oral valacyclovir and topical ocular lubrication. The disruption of the host's natural immunological barriers, exacerbated by suboptimal contact lens handling, paved the way for subsequent dendritic ulceration. This case report shows how the poor handling of contact lens can result in a compromised cornea, causing HSV reactivation.

KEYWORDS: Herpes simplex keratitis, contact lens, Langerhans cells, herpes simplex epithelial keratitis

INTRODUCTION

A member of the alpha herpesvirus family, herpes simplex virus (HSV) progresses through initial exposure, latency, and reactivation stages.[1] Its transmission relies on personal contact with an active carrier, initiating viral invasion and replication at the primary exposure site[2]. Following primary exposure, HSV enters a dormant phase within the host's immune system, primarily in the dorsal root ganglia.[2] HSV infections persist throughout life, are marked by periodic reactivations, and are globally prevalent. The seroprevalence of HSV-1 stands at 19.1% in healthy children, and surges to 51.4% in healthy adults.[3] A 2016 meta-analysis found an annual increment in seroprevalence of 1.02-fold per year of age.[3] Meanwhile, a 2022 meta-analysis disclosed a 10% seroprevalence of HSV-2 in the general population.[4] Traditionally associated with genital herpes, HSV-2 faces competition from a noticeable rise in genital HSV-1 infections among females.[5]

While HSV is treatable, achieving a complete cure remains elusive due to the intrinsic nature of the virus. Individuals commonly grapple with herpetic reactivation, and for patients contending with HSV keratitis, the impact on their quality of life can be substantial, particularly for those experiencing recurrent relapses. Among such cases, a notable decline in visual acuity is the most pronounced detrimental effect.[6]

Viral reactivation is triggered by various internal and external factors including local injury, radiation exposure, disrupted homeostasis, and immunosuppressive therapy.[7] The physiological changes induced by contact lens misuse, including overuse or poor handling, can pose a potential threat to the innate defense system on the ocular surface.[8] This case involves an

unconventional trigger for HSV reactivation, emphasizing the documented association between herpetic keratitis reactivation and contact lens use. It is imperative, however, to differentiate between this scenario and other forms of infectious keratitis, and therefore reduce the risk of misdiagnosing herpetic keratitis in contact lens wearers presenting with dendritic patterns when, in fact, other infectious causes may be at play.

CASE REPORT

A 22-year-old woman presented for an urgent eye examination, having sought medical attention at the hospital three nights prior. The reason for her emergency room visit was eye pain, which she reported occurred following sleeping in her contact lenses for approximately one hour. At the hospital, topical proparacaine hydrochloride ophthalmic solution was administered, and a prescription for ophthalmic moxifloxacin 0.5% as well as an ocular lubricant were provided.

The patient reported that she stored her colored, non-prescription contact lenses in spectacle lens cleaner solution for a few hours before inserting them. She wore them for a few hours, removing them two hours before bedtime. Although symptoms had improved since her hospital visit, she was still moderately light-sensitive with pain, red eyes, epiphora (without coloured discharge), and mild crusting of the lashes in the morning. Her last medical examination had been in the summer of 2023 with unremarkable results. The patient was not pregnant or breastfeeding. The patient denied environmental or medication allergies and tobacco use, and reported a family history of cataracts without mention of glaucoma, visual impairment, or other ocular conditions. Ocular history was unremarkable, with no mention of ocular trauma or surgeries. The patient purchased her contact lenses online, solely for cosmetic purposes, and reported poor contact lens hygiene.

On this visit, the patient's presenting unaided visual acuities were 20/70 in the right eye, which improved to 20/20 with pinhole, and 20/20 in the left. Broad H was associated and unrestricted with dull pain upon eye movements of both eyes (reported 5/10 and 3/10 in the right and left eyes, respectively, especially when returning to primary from extreme lateral gazes). Her external examination was unremarkable with normal confrontation fields, and no evidence of relative afferent pupillary defect. Anterior segment examination revealed no periorbital edema or skin vesicles. Both eyes exhibited mild conjunctival hyperemia, diffuse bulbar conjunctival staining, and grade 3+ corneal staining concentrated around the limbus. A central dendritic lesion with branching was observed in the right eye after the instillation of fluorescein sodium (Fig. 1). No infiltrates or precipitates were detected in either cornea, and the left eye was free of dendritic lesions. Intraocular pressures measured with iCare (11:35AM) were 16 mmHg in the right eye and 15 mmHg in the left. Subsequent dilated posterior segment examination showed healthy optic nerve heads and macular regions with no signs of retinal vasculitis. There was no evidence of retinal necrosis or peripheral retinitis during the peripheral retinal examination in either eye. The vitreous was clear.

Figure 1: *Dendritic ulceration of the right eye at presentation.*

THE FOLLOWING DIFFERENTIAL DIAGNOSES WERE CONSIDERED:

1. Herpes zoster ophthalmicus (HZO)

Varicella zoster virus (VZV) is the causative agent behind both chickenpox and shingles. Chickenpox is an airborne disease that can also spread through contact with skin lesions or blisters.[9] Following the primary infection, the virus enters a dormant state within the dorsal root ganglia. Reactivation of the virus results in replication, local inflammation, and blistering along the dermatome.[9-11] Various triggers can reactivate VZV.[11] These triggers induce a decline in cell-mediated immunity against the virus, ultimately leading to the reactivation of VZV and the onset of shingles or herpes zoster. [11]

The most prevalent manifestation of VZV reactivation is herpes zoster.[12] Typically, it presents with painful vesicular lesions distributed along the dermatome of the trigeminal nerve.[13-15] Predominantly, the thoracic region is affected (> 50%), followed by the face (trigeminal 20% and ophthalmic), cervical (20%), and lumbosacral (11%) regions.[16,17] This condition is more prevalent among the elderly, individuals undergoing immunosuppressive therapy, and those with compromised immune systems.[18]

The differentiation between HZO and HSV keratitis relies on the morphological characteristics of ocular lesions. HZO displays small, elevated dendrites without terminal bulbs, and exhibits minimal fluorescein staining. In contrast, HSV keratitis presents with dendrites as brightly stained ulcers with visible terminal bulbs.[19] Sodium fluorescein staining occurs at the base of the ulceration in HSV keratitis, while Rose Bengal stains the edges.

2. Contact lens-associated microbial keratitis

Contact lens wear is a significant cause of microbial keratitis, encompassing bacterial, fungal, protozoal, and viral aetiologies.[20] Bacterial keratitis, an infection affecting the cornea caused by microorganisms (most often *P. aeruginosa, S. aureus, and S. marcescens*), poses a sight-threatening risk if not promptly treated.[21] Bacterial keratitis is the predominant cause of microbial keratitis, and contributes to 90% of the cases.[22] Multiple risk factors for microbial keratitis, including the type of contact lens, hygiene, handling and disinfection practices, and overuse and misuse of contact lenses, contribute to the development of this condition.[20,23]

Microorganisms responsible for this ocular condition typically come from the wearer's fingertips, lid margins, contaminated water, contact lens case, or cleaning solution.[24] These bacteria adhere to the corneal epithelial cells and penetrate the stroma through the action of exotoxins. These exotoxins are crucial for breaking down the basement membrane and extracellular matrix, resulting in cellular lysis. After this invasion, bacterial proteases contribute to melting of the cornea. The combined impact of bacterial exotoxins and proteases results in stromal destruction and, eventually, vision loss.[24]

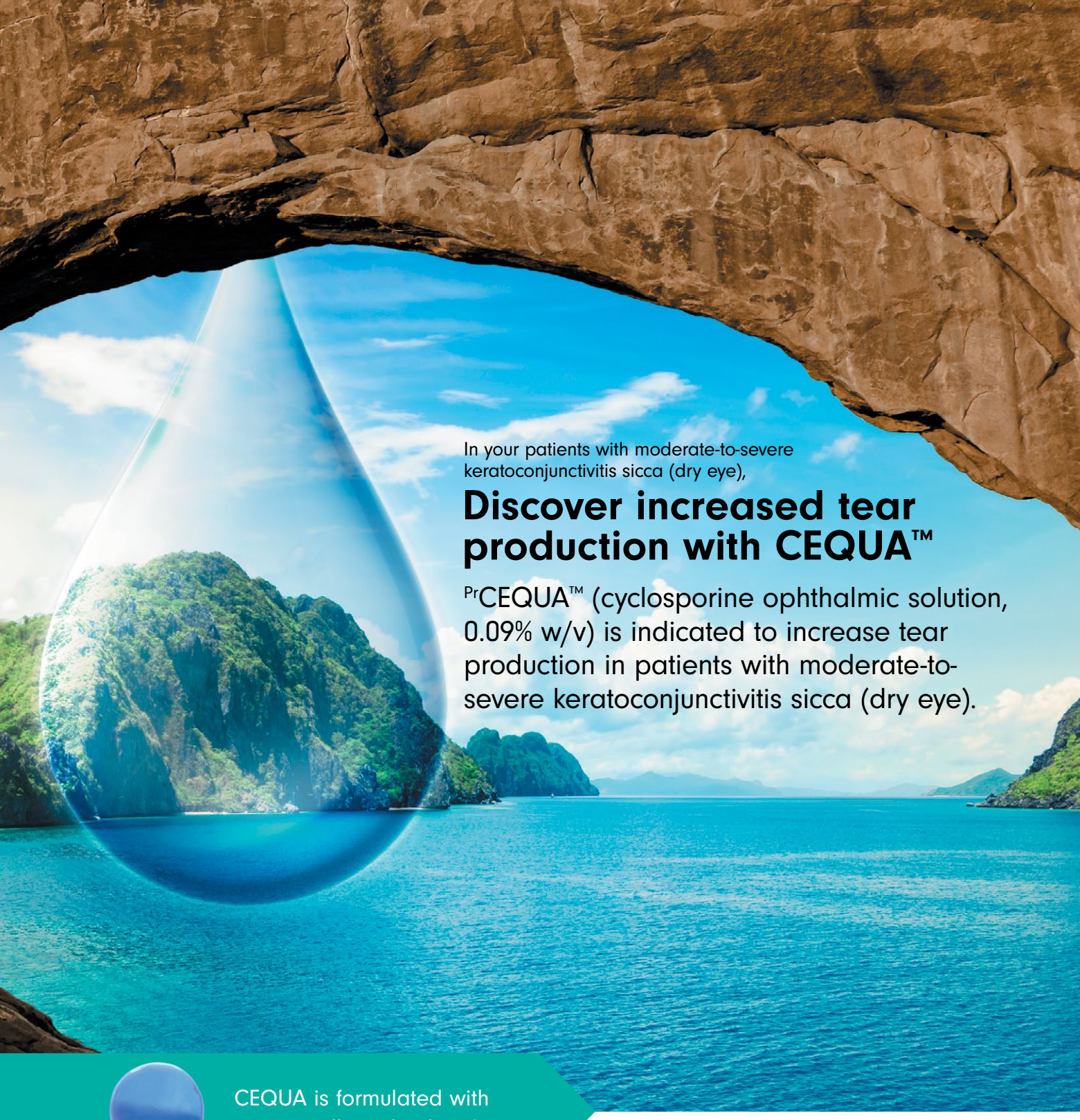
Clinical manifestations of bacterial keratitis include lid edema, matting of lashes, purulent discharge, conjunctivochalasis, hyperemia, and circumlimbal congestion.[19,23] An epithelial defect, stromal edema, and infiltration are some of the corneal signs that may be noted. It can also include Descemet's folds, cells and flare in the anterior chamber, hypopyon, anterior uveitis, posterior synechiae, and, in severe cases, scleritis.[23] The patient's subjective symptoms include red eyes, pain, blurred vision, photophobia, and discharge.

***3. Acanthamoeba* keratitis**

Acanthamoeba keratitis is an ocular infection that is usually linked to the mishandling of contact lenses or exposure to contaminated water, predominantly seen in individuals with compromised corneal integrity.[25] *Acanthamoeba* species are present in soil, dust, air, and water, with a widespread distribution in the environment and the ability to adhere to diverse materials.[26] *Acanthamoeba* keratitis commences with attachment of the species to contact lenses, followed by their transfer to the cornea and adhesion to its surface.[26,27] This process is followed by disruption of the corneal epithelial barrier, infiltration into the stroma, and the onset of necrosis, potentially leading to blindness.[26]

While contact with *Acanthamoeba* is common, infections caused by it are not. When healthy individuals come into contact with *Acanthamoeba*, this triggers a humoral response against the protozoa.[26] The natural tear film possesses innate immune defences capable of dissolving and eliminating microorganisms.[26,28] Immunoglobulin A (IgA) affects *Acanthamoeba*, hindering its adhesion to the corneal epithelium.[26] Neutrophils and macrophages destroy trophozoites and inhibit their adherence to the epithelium.[26]

Clinical manifestations often involve excessive tearing, photophobia, reduced visual acuity, a red eye, and intense pain that surpasses the severity of ocular findings.[19] The pain is linked to the inflammatory process, and its intensity hinges on which corneal nerves are affected.[26] Initial clinical signs include punctate epithelial erosions, pseudo-dendrites



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(Chameleon-like epithelial changes), subepithelial opacities, circumlimbal injection, microcysts, and microerosions. As the disease progresses, it may result in neovascularization, anterior stromal infiltration, and scarring.[19,25,26,29] Over time, these infiltrates tend to amalgamate, forming a distinct ring pattern.[25,29]

4. Herpes simplex virus keratitis (Final Diagnosis)

A conclusive diagnosis of HSV epithelial keratitis of the right eye and toxic keratopathy of both eyes due to exposure to spectacle lens cleaner solution was made. The patient was instructed to continue the course of topical moxifloxacin 0.5% and treatment was initiated with ocular lubrication and valacyclovir 500mg, three times a day for ten days. Follow-up examinations were made after two and four days, and a significant improvement was noted at each appointment. She presented for her final follow-up after 10 days with a complete resolution of her symptoms. Her unaided visual acuities were 20/20 in each eye, with no signs of toxic keratopathy or dendrites.

DISCUSSION

HSV follows a progression involving initial exposure, latency, and reactivation.[1] The transmission of HSV infection relies on personal contact with an individual actively harbouring the virus. This journey begins with initial exposure, triggering of viral invasion, and intracellular replication at the primary exposure site.[2]

Post-primary exposure, the virus enters a dormant phase within the dorsal root ganglia of the host's immune system, primarily in the trigeminal and sacral ganglia.[2] Recurrent HSV is not indicative of reinfection but rather a consequence of viral reactivation. While spontaneous recurrences are feasible, various internal and external triggers may instigate the transition from a dormant herpesvirus to a proliferative state.[2]

Factors such as ocular surgery, radiation exposure, topical ophthalmic medications, ocular irritants, disrupted homeostasis (i.e., stress), and immunosuppressive therapy serve as risk factors for HSV reactivation.[7] Once reactivated, the virus traverses sensory neurons to mucocutaneous sites, undergoing replication and potentially recurrence.[2]

HSV has two subtypes, HSV-1 and HSV-2, with HSV-1 primarily manifesting in the oropharyngeal mucosa, while HSV-2 is predominantly associated with sexually transmitted infections.[2,30,31] Notably, recent studies have indicated the presence of HSV-1 in the genital tract and HSV-2 in the mouth, attributed to oral-genital sex; however, recurrence or recrudescence from such transmission is infrequent [5,32]. Despite the potential for HSV-1 and HSV-2 to result in oral infections, the overwhelming majority of cases can be attributed to HSV-1.[33] Notably, most HSV-1-induced infections exhibit subclinical characteristics, and are often unnoticed.[33]

As of 2016, the World Health Organization estimated global seroprevalence rates of 67% for HSV-1 and 13% for HSV-2 among individuals under 50 years old.[34] The consequences of recurrent HSV can range from asymptomatic to mild symp-

toms, which can become life-threatening. The outcome of the infection or reactivation is contingent upon the interplay between HSV and the host's immune system.[35]

HSV infections can manifest as skin or mucosa infections, affecting various regions such as the face and mouth (orofacial herpes), genitalia (genital herpes), or hands (herpetic whitlow).[32,36,37] Additionally, infections may extend to the eyes (herpetic keratitis) and invade the central nervous system, leading to encephalitis and meningitis.[36]

HSV keratitis is the most prevalent corneal infection, with the ability to affect the epithelium, stroma, or endothelium. HSV is capable of inducing conditions such as anterior uveitis, acute retinal necrosis, or progressive outer retinal necrosis.[38-40]

The diagnosis of HSV epithelial keratitis primarily relies on its clinical presentation during slit lamp examination. Classic signs include unilateral dendritic lesions featuring terminal bulbs, where the edges of the lesion and terminal end bulbs stain with Lissamine Green or Rose Bengal. Moreover, the central defect will stain with sodium fluorescein.[41] Progression may lead to a geographic ulcer characterized by slower healing and more significant inflammation.[38-40] Dendrites or geographic ulcers typically exhibit heaped-up edges comprised of epithelial cells.

Common symptoms of HSV keratitis are red eyes, discharge, irritation, pain, itch, and photophobia.[19,30] Typically, HSV keratitis manifests as a unilateral disease, but instances of bilateral HSV keratitis, though uncommon, have been observed, particularly in immunocompromised patients (i.e., HIV).[42,43]

While the diagnosis of HSV epithelial keratitis is often made clinically, without the need for laboratory confirmation, the clinical features of herpes simplex stromal keratitis can be less distinct. Diagnostic tests are available in cases of true diagnostic uncertainty. Techniques such as scraping of corneal lesions for Giemsa stain, polymerase chain reaction (PCR) tests, or immunofluorescence antibody assays (IFA) can be valuable for confirming a herpetic infection.[30,44,45] Giemsa stain targets multinucleated giant cells, PCR detects HSV-1 DNA, and IFA identifies HSV-1 antigen.[44] A study indicated that the sensitivities of IFA and PCR for HSV keratitis were 78.6% and 81.2%, respectively.[44] Both PCR and IFA were found to be equally sensitive, though false-positives remain a common challenge in PCR testing.[44]

Sleeping in contact lenses is known to be a high-risk behaviour that carries a significant relative risk for corneal infection, regardless of the lens material and frequency of use.[46] Contact lens use introduces localized stress to the cornea, precipitating alterations in multiple facets of the immune defence at the ocular surface.[47,48] Stressors associated with contact lens application encompass mechanical hypoxia, modifications in tear dynamics, inflammatory responses, and biofilm formation.[49]

Comprising both innate and adaptive immune systems, the ocular surface deploys innate defences as the initial response to foreign pathogens, acting in a non-discriminatory manner.[50] Physical barriers, such as the orbital bone and eyelids, safeguard against traumatic events. At the same time, the tear film serves as a multifaceted defence by lubricating the ocular surface, supplying nutrients, and acting as a chemical barrier against external pathogens.[50] This protective mechanism extends to flushing foreign particles away from the ocular surface and facilitates the transportation of anti-microbial proteins and immunoglobulins (IgA and IgG) to prevent infections.[28,50]

Corneal epithelial cells function as physical barriers due to their tight junctions, and secrete cytokines, further fortifying the defence against microbial invasion.[51] The effects of hypoxia on corneal epithelium from contact lens wear has been reported previously, with a reduction of oxygen supply ranging from 8 – 15% depending on the material.[52] The normal composition of the cornea undergoes alterations due to contact lens use, inducing local hypoxia that leads to a decreased epithelial metabolic rate, resulting in epithelial thinning and the loss of tight junctions and hemidesmosomes.[52] This shift in normal physiology increases the susceptibility of the cornea to opportunistic infections and may lead to vascularization and hypoesthesia.[53,54]

Adequate oxygen supply is imperative for the metabolic processes of corneal cells, and contact lenses with low oxygen transmissibility constrain this flow, reducing local pH and generating lactic acid.[48] Napping or sleeping while wearing contact lenses leads to hypoxia, and the accumulation of waste products due to diminished overall tear film flow.[48] The chronic irritation and inflammation stemming from the use of contact lenses has the potential to modify the local immune response. Prolonged oxygen deprivation, frequently associated with ill-fitting contact lenses or overuse, can disrupt corneal homeostasis, resulting in corneal edema and elevated susceptibility to infections.[48]

The patient in this case stored non-prescription coloured contact lenses in a spectacle lens cleaning solution composed mostly of water, alcohol, and surfactants.[55] Alcohol and other chemicals pose significant risks as potent irritants capable of inducing allergic contact dermatitis, ocular burns, and damage to mucosal linings.[56] Even brief exposure to alcohol can induce corneal inflammation, edema, alterations in tear film composition, contact dermatitis, and damage to mucosal surfaces.[57] Ethanol, in particular, has been demonstrated to trigger proinflammatory cytokines in the corneal epithelium, potentially predisposing patients to ocular surface diseases.[57]

The corneal immune system, involving Langerhans cells, plays a crucial role in modulating adaptive immune responses.[58] Contact lens use elevates Langerhans cell density in the cornea, predisposing the wearer to an exaggerated immune response to insults including viral infection and reactivation.

Langerhans cells, vital for recognizing and presenting antigens, are scarce in healthy eyes.[58] Their absence during viral infection or reactivation in the central cornea compromises the anti-viral response, leading to limited keratitis development.[58] When viral infection or reactivation occurs in an eye lacking Langerhans cells in the central cornea, the immunopathogenic anti-viral response is curtailed, resulting in either transient or non-existent keratitis development.[59] Langerhans cells can migrate into the cornea from the limbus in response to various stimuli, such as contact lens use.[60] The migration of Langerhans cells into the central cornea before exposure to HSV-1 leads to a more robust and immediate immune response. However, this heightened response is correlated with an increased likelihood and severity of herpetic reactivation.[58]

Although HSV epithelial keratitis is self-limiting, prompt initiation of treatment is essential to minimize viral replication, shorten the disease duration, and reduce the risk of additional complications that could potentially be vision-threatening.[38, 30] The management strategy for HSV keratitis commonly incorporates both topical and oral antiviral medications. Furthermore, corneal debridement, a method discussed in earlier literature, is frequently employed.[30,61] By eliminating virally infected cells, corneal debridement promotes corneal epithelial regrowth and decreases the viral load.[38] Nonetheless, relying on this strategy as the exclusive therapy for HSV epithelial keratitis is not recommended.[62] Although the combined use of debridement and antiviral therapy has been linked to improved corneal recovery, it has not been shown to be superior to using a single antiviral medication in corneal epithelial healing at the 14-day mark.[61] When antivirals are either contraindicated or unavailable, debridement might be considered as an alternative. It is important to note that this treatment option was not administered in-office; instead, an oral antiviral medication was prescribed.

The primary antiviral drugs prescribed as a first line of defence include both oral and topical ophthalmic eye drops. Oral medications such as acyclovir, valacyclovir, and famciclovir are commonly used. In cases of active herpes infection, there is a general lack of evidence of significant differences in the effectiveness of oral antiviral medications. Notably, valacyclovir appears to have superior bioavailability compared to acyclovir.[63,64] Reducing the valacyclovir dosage has been shown to enhance adherence to treatment and decrease potential financial barriers.[65]

The U.S. Food and Drug Administration-approved topical medications for HSV epithelial keratitis include trifluridine 1%, and ganciclovir 0.15%.[66,67] Trifluridine was previously widely used as the established therapeutic approach for managing herpetic corneal ulcers before the introduction of ganciclovir. However, trifluridine has certain limitations, including dosage inconvenience, and a recommendation against extended usage (more than 21 days) due to potential side effects such as contact dermatitis (10%), punctate epithelial keratopathy, punctal occlusion, conjunctival cicatrization, and inhibition of corneal epithelial wound healing.[68,69]

The use of topical antivirals was limited due to the lack of availability in Canada. The recent introduction of ganciclovir ophthalmic gel 0.15%, released on September 26, 2023, now provides ophthalmologists and family doctors in Canada with a readily accessible option for treating HSV keratitis.[70]

The treatment landscape for HSV keratitis has evolved significantly with the Herpetic Eye Disease Study (HEDS) randomized clinical trials. HEDS focused on the use of oral antivirals to prevent epithelial and stromal HSV keratitis reactivation.[71,72] In patients with a history of only epithelial keratitis, prophylaxis consisting of acyclovir 400mg twice a day reduces the risk of recurrence by 40%, whereas a reduction of 70% is noted in patients with recurrent stromal keratitis. For patients with no prior history of HSV stromal keratitis, prophylaxis did not significantly reduce the risk of developing recurrent episodes of stromal keratitis.[71,72]

While Mucci et al. found higher recurrence rates in contact lens wearers (0.4 episodes/year) compared to non-contact lens wearers (0.2 episodes/year), HEDS did not find a clear association between contact lens use and HSV epithelial keratitis recurrence.[73] Current research does not provide a clear mechanism for how contact lens use may increase the risk of HSV epithelial keratitis. Some suggested mechanisms of action include possible deviation of the immune response at the ocular surface, microtrauma and inflammation, as well as neurotrophic effects.

CONCLUSION

This case highlights the reactivation of HSV in a young, otherwise healthy female, resulting in unilateral HSV epithelial keratitis, and bilateral toxic keratopathy marked by symptoms of pain, photophobia, and epiphora. Treatment involved oral antiviral therapy, topical antibiotics, and copious lubrication. Notably, corneal compromise in such cases can markedly affect corneal immune responses, directly impacting the innate defenses of the ocular surface against HSV. ●

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