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Herpes Simplex Virus Keratitis – Diagnostic and Therapeutic Challenges

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Summary: Herpes simplex virus keratitis is one of the leading causes of blindness worldwide. The observed inflammatory changes may result from a primary ocular infection or, more commonly, from recurrent reactivation of the virus, which remains latent in the trigeminal ganglion. The diagnosis of clinically active herpetic eye disease is based primarily on the characteristic clinical features of the lesions. Clinical manifestations include epithelial keratitis, stromal keratitis with or without ulceration, and endothelial keratitis. In addition, herpes simplex virus is a frequent cause of neurotrophic keratopathy. Establishing the diagnosis may be particularly challenging in cases of long-standing or frequently recurrent lesions, as well as in patients with coexisting systemic conditions that impair immune function. Currently, the cornerstone of therapy for herpetic keratitis – tailored to the clinical form of the disease – consists of antiviral agents and topical corticosteroids. This paper summarizes current knowledge on the pathophysiology, diagnosis, and treatment of herpes simplex virus keratitis and presents the authors' own experience with the broad spectrum of clinical manifestations observed in this condition.

Key words: herpes simplex, keratitis, dendritic keratitis, cornea.

Introduction

Herpes simplex virus keratitis is the most common infectious cause of corneal ulceration and vision loss worldwide [1]. Humans are the only natural host of the herpes simplex virus (HSV), with HSV-1 and HSV-2 being the most prevalent types. Studies evaluating the presence of HSV-1 DNA in the trigeminal ganglion indicate that at least 90% of the global population is infected with latent virus by the age of 60 [2]. Transmission of herpes simplex virus occurs through contact with active oral or labial lesions, or through exposure to infected saliva from asymptomatic carriers [3]. Primary ocular infection with HSV may occur at any time during life. Research has shown that the mean age of first ocular HSV-1 infection is 37.4 years in the United States and 25 years in the United Kingdom [4, 5]. Most primary infections are unrecognized or asymptomatic. Primary herpes simplex keratitis may present as mild, self-limiting blepharoconjunctivitis accompanied by inflammatory vesicles or ulcerations with corneal epithelial lesions [6]. Mild fever, malaise, or upper respiratory tract infection may also occur [7]. In a multicenter study conducted in France, the most common forms of herpetic keratitis were dendritic keratitis (56.3%), stromal keratitis (29.5%), and geographic keratitis (9.8%). Ocular changes associated with keratitis were observed in 35.0% of patients: conjunctivitis (18.8%), uveitis (11.8%), and/or eyelid involvement (8.6%) [8]. After primary contact, the virus may establish a permanent latent infection in the trigeminal ganglion, serving as a reservoir for future reactivations along any branch of the trigeminal nerve [9]. Recurrent ocular infection manifests as inflammation of the ocular adnexa or keratitis. In the preventive Herpetic Eye Disease Study (HEDS), the majority of recurrences involved the cornea, with 37% affecting the epithelium and 46% the stroma. Recurrent episodes of herpetic simplex keratitis account for most ocular manifestations of HSV infection seen in routine clinical practice. The recurrent nature of the disease, particularly when involving the corneal stroma and accompanied by an immunopathological process, may lead to scarring, neovascularization, endothelial dysfunction, and vision loss [10].

Clinical manifestations of herpetic keratitis

Epithelial keratitis

Epithelial keratitis, i.e. the most common and recurrent subtype, presents as scattered granular spots (Fig. 1) that rapidly coalesce into dendritic lesions [11]. Viral replication observed within the epithelial layer, leading to cell lysis and desquamation, contributes to the formation of dendritic ulcers [12]. After 5–7 days, slit-lamp examination reveals a characteristic branching lesion with terminal bulbs, edematous margins, and infiltration of intraepithelial inflammatory cells [13]. Topical fluorescein staining visualizes the dendritic lesions, as shown in Figure 2. The virus replicates predominantly at the edges and terminal ends of these dendritic lesions, which may enlarge and evolve into geographic ulcers characterized by extensive areas of necrotic cells (Fig. 3). After healing of the epithelial lesions, mild subepithelial opacity may develop, along with scarring.

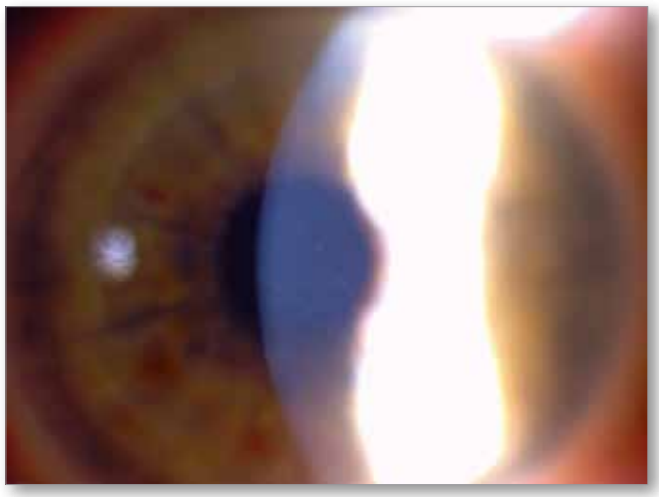

Fig. 1. HSV epithelial keratitis presenting as subtle, diffuse epithelial haze.

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Fig. 2. Dendritic infiltrates visible on slit-lamp examination with a cobalt filter after fluorescein staining.

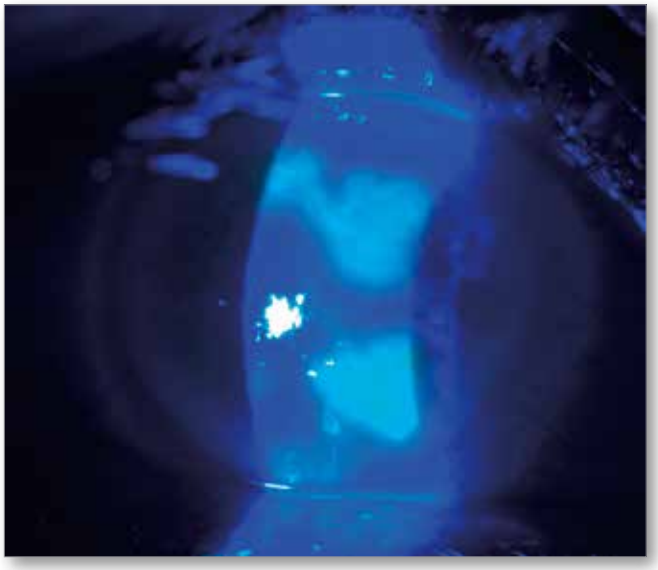

Fig. 3. Geographic corneal epithelial ulceration.

Stromal keratitis

Herpetic epithelial keratitis results from direct infection of corneal epithelial cells, whereas HSV stromal keratitis is primarily attributed to host immune mechanisms, with deposition of immune complexes and complement in the cornea [14]. The necrotizing form of the disease is characterized by infiltration of inflammatory cells, including lymphocytes, plasma cells, and neutrophils, leading to grey, white, or opaque lesions accompanied by stromal edema and necrosis [15]. In contrast, the non-necrotizing (interstitial) form of stromal keratitis presents with more diffuse stromal inflammation without significant necrosis. The formation of fibrovascular tissue and neovascularization, resulting in permanent corneal opacity, are common to both forms [16]. Complications of recurrent herpetic keratitis in the form of fibrovascular tissue formation are shown in Figure 4.

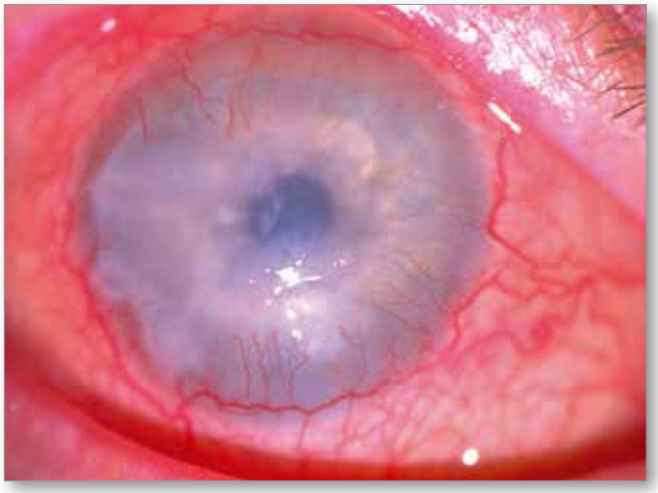

Fig. 4. Recurrent, severe herpetic keratitis complicated by the formation of fibrovascular tissue.

Endothelial keratitis

Endothelial keratitis caused by herpes simplex virus is relatively rare and usually occurs independently of other forms of HSV keratitis. This form of HSV keratitis is often referred to as disciform keratitis, owing to a discrete, well-demarcated, round or oval area of corneal deposits with overlying corneal edema. However, corneal endotheliitis may also involve the entire cornea, in which case the term 'disciform' does not fully describe the disorder [10]. Inflammatory cells induced by HSV infection circulating in the aqueous humor form deposits on the endothelium. Corneal edema and haze may be present due to endothelial dysfunction and reduced endothelial cell density [17].

Permanent corneal changes caused by HSV infection are a common indication for keratoplasty. The two main causes of graft failure after penetrating keratoplasty in patients with herpes simplex virus-related eye disease are viral reactivation, leading to clinical recurrence of herpetic keratitis, and simple graft rejection [18]. Figure 5 illustrates a transparent corneal flap three years after penetrating keratoplasty (a) and herpetic disease recurrence four years after the procedure (b). The recurrence rate of HSV keratitis after penetrating keratoplasty appears to be inversely proportional to the duration of oral acyclovir therapy. One year after keratoplasty, the recurrence rate among patients treated with this drug for three weeks is 30%, for three months – 18%, for six months – 5.7%, and for one year – between 0 and 5%. Although the recurrence rate in groups treated for six months and one year is similar, treating patients for at least a full year with prophylactic oral antiviral agents may be beneficial, as most recurrences of HSV keratitis occur within the first year after keratoplasty [10].

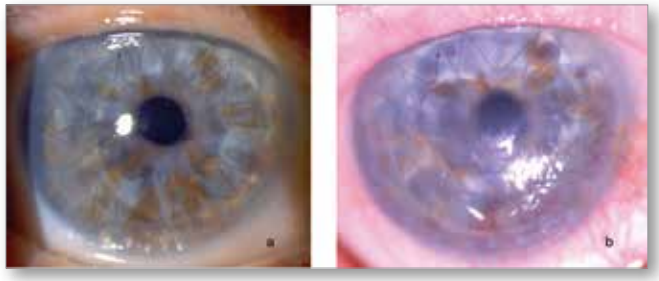

Fig. 5. Transparent corneal graft three years after penetrating keratoplasty (a) and graft disease caused by recurrence of herpetic disease four years after the procedure (b).

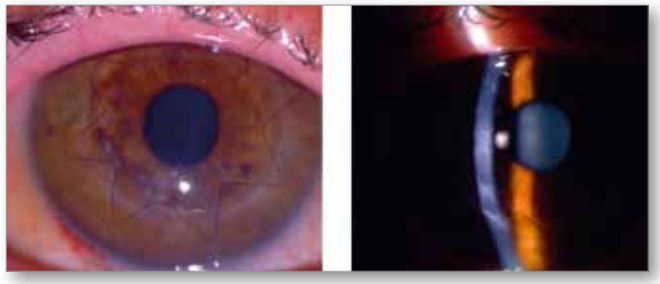

Fig. 6. Endothelial deposits and slight haze of the corneal graft stroma one year after penetrating keratoplasty due to HSV-induced changes.

The most common form of graft rejection after penetrating keratoplasty is endothelial rejection, occurring in 50% of cases [19]. Changes including anterior chamber reaction and endothelial deposits accompanied by corneal edema are observed both in herpetic endothelial keratitis and in endothelial graft rejection, making differentiation between these two conditions a diagnostic challenge. Figure 6 shows a case of such changes occurring after penetrating keratoplasty due to HSV-induced lesions. The changes were observed one year after the procedure (oral acyclovir prophylaxis had been discontinued one month earlier). Improvement in visual acuity and corneal condition was achieved after reintroduction of antiviral therapy along with intensive topical steroid treatment.

Complications of herpetic eye disease

By attacking the trigeminal ganglia, HSV causes reduced corneal sensitivity, probably due to decreased density of the subbasal nerve plexus [20]. Loss of sensation disrupts the natural blink reflex, leading to epithelial damage, increased risk of superinfection, and corneal malacia. A non-healing epithelial defect may be associated with stromal malacia and perforation due to lack of reepithelialization resulting from corneal anesthesia, which is often exacerbated by drug toxicity [21]. Figure 7 presents a case of HSV-induced neurotrophic keratopathy in a female patient chronically treated with topical antiviral agents. In this patient, improvement in corneal epithelialization was achieved following the use of autologous serum eye drops.

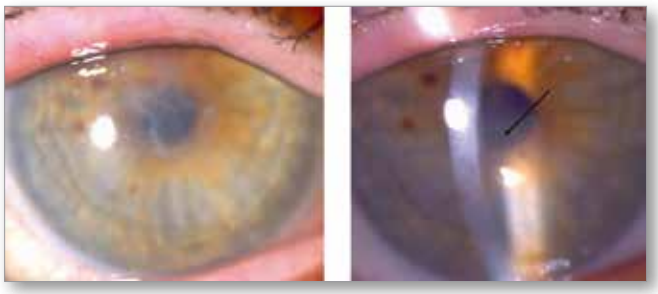

Fig. 7. Lesions occurring at different time points caused by recurrent HSV keratitis in the same patient, complicated by the development of neurotrophic keratopathy with a central corneal epithelial defect (arrow).

Chronic corneal epithelial defects are also observed in cases not associated with HSV infection. Figure 8 shows corneal changes mimicking those induced by HSV in patients with a long history of topical hypotensive therapy for glaucomatous neuropathy, in whom non-healing corneal erosions were found following cyclophotodestruction. Radiation-induced keratopathy may also contribute to the development of epithelial regeneration lines and neurotrophic changes that mimic epithelial alterations typical of herpetic infection. Figure 9 shows the condition of the eye after radiotherapy for maxillary sinus carcinoma. The observed dendrite-like lesions improved after initiation of autologous serum eye drops and periocular injections of methylprednisolone.

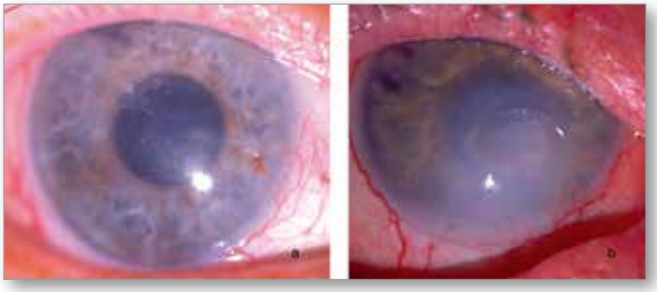

Fig. 8. Corneal changes mimicking HSV infection in patients after cyclophotodestruction, presenting as dendrite-like lesions (a) and corneal ulceration (b).

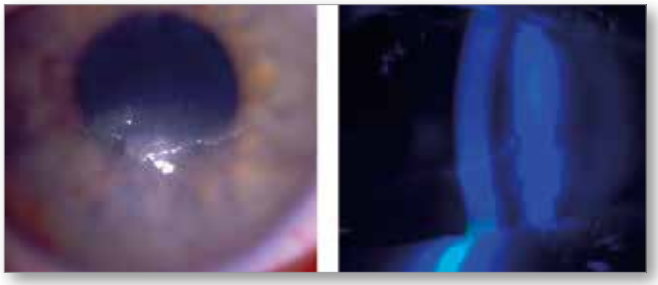

Fig. 9. Dendrite-like corneal lesions in a patient treated with radiotherapy for maxillary sinus carcinoma.

Diagnostic procedure

The diagnosis of herpetic keratitis is established primarily on the basis of the clinical appearance observed during slit-lamp examination. Misdiagnosis is not uncommon, as other pathogens may produce similar manifestations. Amoebic and fungal infections may be misidentified as HSV keratitis. Figure 10 illustrates a case of recurrent viral keratitis with coexisting Acanthamoeba infection, showing HSV-typical changes at the subepithelial nerve plexus level on confocal microscopy, along with amoeba cysts at the epithelial level.

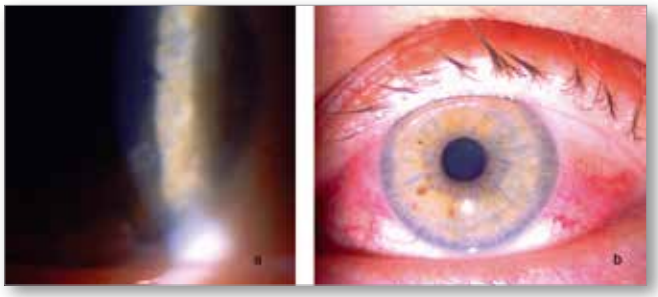

Fig. 10. Granular corneal epithelial changes (a) in a female patient with recurrent viral keratitis and concomitant Acanthamoeba infection with episcleritis (b), a condition frequently accompanying amoebic keratitis.

In cases of atypical epithelial lesions, polymerase chain reaction (PCR) testing is used to confirm herpes simplex keratitis. The method is less useful in identifying immune-mediated HSV keratitis. Moreover, the test requires corneal scrapings, which may be impossible in cases of corneal thinning due to recurrent inflammation. An alternative assessment of viremia based on tear analysis carries a risk of false-negative results, since viral presence in tears decreases during the course of the disease [22]. Viral culture is considered the gold standard for identifying HSV infection; however, it is time-consuming and typically underestimates the number of patients whose disease is caused by HSV [23]. One potential drawback of using PCR in clinical settings is its inability to distinguish between viable and non-viable viral genetic material. This limitation may have implications for its clinical application, particularly when assessing the effectiveness of treatment regimens [24]. In vivo confocal microscopy enables the observation of corneal structural abnormalities and the detection of immune cells whose presence results from HSV infection. This method is characterized by limited resolution, does not allow visualization of viral particles, and the diagnostic criteria for HSV keratitis can rely solely on histological changes in the cornea [24].

Factors that alter the clinical presentation and influence diagnosis include disease duration, systemic comorbidities, prior medication use, and corneal transplantation. In patients with atopy, HSV keratitis more often presents bilaterally and with a severe clinical course [10]. Organ transplant recipients are more susceptible to infection and reactivation of HSV. Several case series con-

firm the association between immunosuppression following organ transplantation and recurrence of ocular HSV infection [10]. Figure 10 presents a case of severe HSV keratitis in a female patient receiving immunosuppressive treatment (everolimus) following liver transplantation.

Fig. 11. Severe HSV keratitis in a patient receiving immunosuppressive therapy, before (a) and after initiation of antiviral treatment (b), with residual permanent stromal haze.

Treatment

Most cases of HSV keratitis are self-limiting without treatment; however, this may result in prolonged healing time, scarring, and the development of pathological neovascularization. Treatment of herpes simplex keratitis is based primarily on the administration of nucleoside analogues. Acyclovir has poor bioavailability and requires high doses with increased frequency of administration. Valacyclovir demonstrates improved bioavailability, is administered less frequently, and may therefore enhance patient adherence to treatment. Acyclovir and valacyclovir may cause nausea, vomiting, and diarrhea. Although ganciclovir has fewer side effects, it can cause blurred vision, punctate keratitis, and eye irritation. Prolonged treatment with these nucleoside analogues carries a risk of resistance, particularly in immunocompromised patients. Second-line therapy includes foscarnet and cidofovir, which exhibit lower specificity for viral DNA and considerable toxicity [25].

Three randomized studies have shown that the available topical antiviral agents (3% acyclovir ointment and 0.15% ganciclovir gel) are equally effective in treating epithelial keratitis. Oral antiviral agents appear to be as effective as topical antivirals in the management of HSV epithelial keratitis. There is no evidence that simultaneous use of two antiviral agents, whether topical or oral, accelerates healing of HSV epithelial keratitis. Debridement of the lesion may be considered only in cases of contraindications to or unavailability of antiviral medications [10].

The preferred treatment for HSV stromal keratitis and endothelial keratitis is based on topical corticosteroids combined with an oral antiviral agent for at least ten weeks. The treatment should be adjusted according to the presence or absence of corneal epithelial ulceration [10].

The classification of clinical forms and the guidelines for antiviral and anti-inflammatory treatment of herpes simplex kera-

Form of herpetic keratitis	Alternative nomenclature	Treatment
Epithelial keratitis	Dendritic keratitis Geographic ulceration	Antiviral (topical/oral)
Stromal keratitis without ulceration	Non-necrotizing keratitis Endothelial keratitis Immune keratitis	Topical steroid therapy + oral antiviral medication at a prophylactic dose
Stromal keratitis with ulceration	Necrotizing keratitis	Topical steroid therapy + oral antiviral medication at a therapeutic dose
Endothelial keratitis	Disciform keratitis	

Tab. I. Classification and treatment of herpes simplex keratitis.

Epithelial keratitis	Dendritic	Geographic
ACICLOVIR p.o.	400 mg 3–5 times daily for 7–10 days	800 mg 3–5 times daily for 14–21 days
VALACICLOVIR p.o.	500 mg twice daily for 7–10 days	1 g 3 times daily for 14–21 days
ACICLOVIR ointment	5 times daily, continue at least 3 days after lesion healing	
GANCICLOVIR gel	5 times daily until healing, then 3 times daily for 7 days	
Stromal keratitis	**Without ulceration**	**With ulceration**
Topical steroid	6–8 times daily (tapering dose, minimum 10 weeks)	twice daily (tapering dose)
ACICLOVIR p.o.	400 mg twice daily until completion of steroid therapy	800 mg 3–5 times daily for 7–10 days, then 400 mg twice daily until completion of steroid therapy
VALACICLOVIR p.o.	500 mg once daily until completion of steroid therapy	1 g 3 times daily for 7–10 days, then 500 mg once daily until completion of steroid therapy
Endothelial keratitis		
Topical steroid	6–8 times daily (tapering dose)	
ACICLOVIR p.o.	400 mg 3–5 times daily for 7–10 days, then 400 mg twice daily until completion of steroid therapy	
VALACICLOVIR p.o.	500 mg twice daily for 7–10 days, then 500 mg once daily until completion of steroid therapy	

Tab. II. Antiviral therapy and topical steroid treatment of HSV keratitis.

titis, as approved by the American Academy of Ophthalmology, are summarized in Tables I and II. Table II also includes acyclovir in ointment form, with dosing consistent with the Summary of Product Characteristics (the preparation is not available in the United States).

Conclusions

Primary infection of the eye and ocular adnexa with herpes simplex virus results from direct exposure of the host's mucous membranes to infectious material. Reactivation of the infection in the cornea can lead to recurrent keratitis with complications such as scarring, pathological neovascularization, and, in severe cases, permanent vision loss. Diagnosis is based primarily on clinical presentation; however, atypical disease course, coexisting ocular disorders, and systemic conditions may complicate accurate diagnosis. Antiviral and anti-inflammatory therapy must be tailored to the clinical manifestations of herpes simplex keratitis.

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