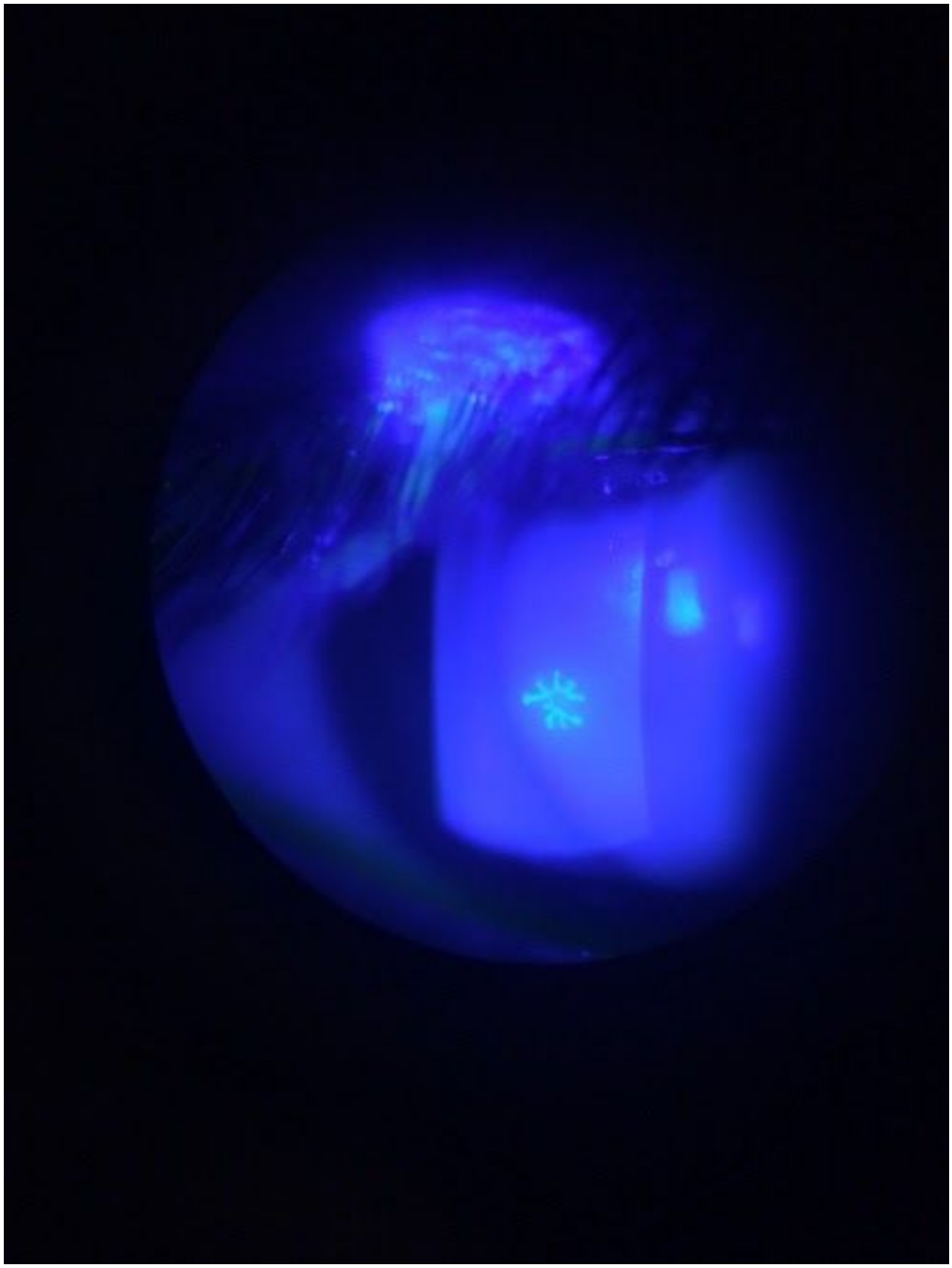
Herpes Simplex Epithelial Keratitis



HSV dendritic lesion with terminal bulbs

Disease Entity

Herpes simplex virus (HSV) is a very common infection that has been reported to be present in the trigeminal ganglion of nearly 100% of patients greater than age 60 at autopsy. In regard to ocular disease, herpes simplex type 1 (HSV- I) and HSV- II may cause blepharoconjunctivitis, epithelial keratitis, stromal keratitis (necrotizing or non-necrotizing), iridocyclitis, and/or retinitis. In the United States, there are approximately 60,000 cases of new and recurrent cases of HSV keratitis yearly.

This EyeWiki will focus on corneal manifestations of the herpes simplex virus.

Disease

Herpetic keratitis can be unilateral or, more rarely, bilateral (the latter being more common in patients with atopy). Age, geographic location, and socioeconomic status appear to affect the prevalence of disease. HSV can affect all layers of the cornea and may be accompanied by a blepharoconjunctivitis, which involves lesions of the eyelid and a follicular response of the conjunctiva. Characteristically, HSV epithelial keratitis presents with classic dendritic lesions with terminal bulbs. Recurrent activations within the sensory ganglion can result in cornea scarring, necrosis, and decreased sensation (neurotrophic cornea). HSV keratitis is a major cause of cornea blindness worldwide.

Etiology

HSV keratitis is caused by the herpes simplex virus, a double- stranded DNA virus made up of an icosahedral shaped capsid surrounding a core of DNA and phosphoproteins of viral chromatin. HSV-I and HSV- II are differentiated by virus specific antigens. HSV- I typically affects the orofacial region while HSV- II usually causes genital infections, though studies have shown that both viruses may affect either location.

Risk Factors

Risk factors for development of primary HSV involve direct contact with infected secretions or lesions.

Risk factors for reactivation of disease have been postulated to include:

- Sunlight
- Trauma
- Heat
- Menstruation
- Stress
- Trigeminal nerve manipulation
- Infectious disease and immunocompromised states.

General Pathology

Corneal scrapings of HSV keratitis prepared with Giemsa stain may reveal the presence of intranuclear viral inclusion bodies. Multinucleated giant cells may also be found. With complete stromal inflammation, a granulomatous reaction may be seen, usually at the level of Descemet's membrane.

Pathophysiology

Ocular herpetic disease is more frequently caused by HSV- I, which is presumed to gain access to the cornea via the trigeminal nerve from an oral infection or direct contact of infected secretions. Initial infection typically remains asymptomatic, but patients may present with an acute follicular conjunctivitis and an upper respiratory infection. After the primary infection, the virus travels via sensory nerve axons to establish a latent infection in the trinomial ganglion where it resides permanently. The virus is then capable of reactivation along any branch of the trigeminal ganglion to cause ocular morbidity.

Primary prevention

Prevention of herpetic infection includes avoidance of direct contact with lesions and secretions of a patient with active HSV.

Diagnosis

Diagnosis of HSV is usually made clinically, however, definitive diagnosis can be made using tissue culture or serum antigen detection techniques. Fluorescent antibody (FAB) testing involving impression cytology using nitrocellulose membrane or a cornea smear. A Tzanck smear can reveal multinucleated giant cells and intranuclear eosinophilic inclusion bodies. Serum antibody testing is typically of limited use.

History

Key aspects to inquire about in the history of patients with suspected HSV include past infections (history of recurrent "red eye", particularly unilateral), underlying systemic diseases, immunosuppression or immunocompromised state, history of eyelid lesions, and history of oral and genital ulcers.

Physical examination

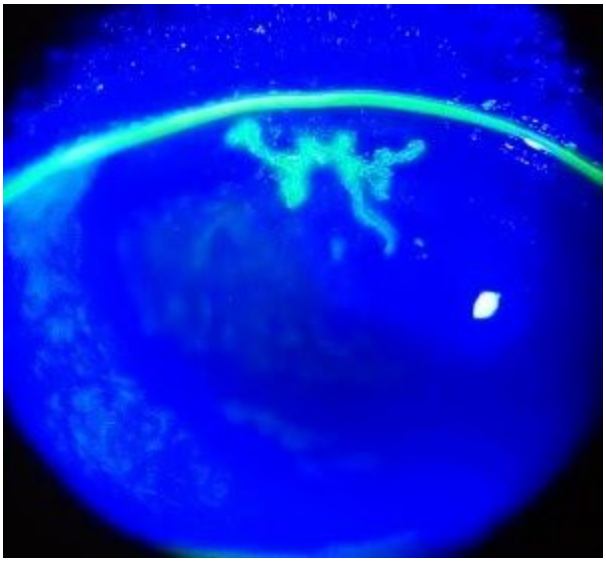
In addition to a standard biomicroscopy, special attention should be paid to the presence of a preauricular lymph node, vesicular lesions on the lids or adnexa, bulbar follicles, decreased corneal sensation, and most notably the presence of epithelial dendrites on the cornea.

For primary HSV keratitis, it is more common for patients to present with a blepharoconjunctivitis than with cornea involvement.

Recurrent HSV keratitis can present as epithelial keratitis. The earliest sign of epithelial disease include raised clear vesicles that later coalesce to form the classic dendritic lesion. The dendritic

ulcer, the dichotomous branching cornea lesion, can be stained with fluorescein and is the hallmark of HSV epithelial keratitis. These epithelial lesions represent active replicating virus. As the dendritic ulcer may evolve into a geographic ulceration of the cornea, especially in patients with compromised immunity or on topical steroids. Patients may also present with marginal keratitis. HSV keratitis has a recurrence rate of 40% at five years.

Signs



Dendritic corneal ulcer due to recurrent keratitis by Herpes Simplex Virus

The hallmark of HSV keratitis is the presence of multiple small branching epithelial dendrites on the surface of the cornea, although often times it first presents as a coarse, punctuate epithelial keratitis (and may be mistaken for a viral keratitis). The HSV dendrite possesses terminal bulbs (that distinguish it from HZO) and follows the nerve pattern of the cornea.

Symptoms

Typically, patients with HSV keratitis present with blurry vision, extreme photophobia, pain, redness, and tearing.

Clinical diagnosis

The clinical diagnosis of HSV may be suggested by the presence of the multiple arborizing dendritic epithelial ulcers with terminal bulbs. The bed of the ulcer stains with fluorescein, while the swollen corneal epithelium at the edge of the ulcer typically stains with rose bengal. Several dendrites may

also coalesce to form a geographic epithelial ulcer. In addition, there may be mild conjunctival injection, ciliary flush, mild stromal edema and subepithelial white blood cell infiltration. Following resolution of the primary infection, a "ghost dendrite" may be visible just beneath the prior area of epithelial ulceration.

Diagnostic procedures

The diagnosis of HSV is often made clinically, however, laboratory tests are available to confirm the diagnosis in difficult cases (and in all cases of neonatal herpetic infection). Serologic testing may be performed but is usually not helpful in recurrent disease as most adults are laterally infected with HSV. However, conjunctival scrapings, impression cytology specimens, and scrapings from vesicular lesions on the skin may be tested by cytology, culture, or polymerase chain reaction (PCR) for the presence of HSV.

Laboratory test

See Diagnostic Procedures

Differential diagnosis

The differential diagnosis of HSV includes herpes zoster ophthalmicus, viral keratitis (usually adenovirus), neurotrophic keratopathy, epithelial regeneration line, iatrogenic (topical drops such as antivirals), acanthamoeba, soft contact lens overwear, microbial keratitis, staphylococcal marginal keratitis, and Thygeson’s superficial punctuate keratitis.

Management

Primary HSV epithelial keratitis usually resolves spontaneously, however, treatment with antiviral medication does indeed shorten the course of the disease and may therefore reduce the long- term complications of HSV.

General treatment

The mainstay of therapy is antiviral treatment either in the form of oral administration of acyclovir or valacyclovir or famciclovir for 10 to 14 days or topical antiviral medications. Topical ganciclovir 0.15% can also be utilized and is approved by the FDA for the treatment of acute herpetic keratitis. It is typically dosed five times a day until the cornea ulcer heals, and then three times a day for another week. Topical therapy with trifluridine 1% eight to nine times a day can also be prescribed, but care must be taken to ensure antiviral drops are discontinued within 10-14 days due to corneal toxicity.

Epithelial debridement of the dendrites may also be utilized in conjunction with antiviral therapy to help reduce viral load. Topical corticosteroids are contraindicated in the treatment of active HSV epithelial keratitis. However, for HSV stromal keratitis, topical corticosteroids should be used in the absence of epithelial disease. According to the Herpetic Eye Disease Study (HEDS), long- term prophylaxis with oral antivirals may decrease the risk of recurrent HSV keratitis.

Medical therapy

Please see General Treatment.

Medical follow up

The patient should be closely monitored and if no response to treatment occurs after 1 week of therapy, the possibility of resistance to antiviral therapy, antiviral toxicity, neurotrophic disease, poor compliance with medication or an alternative diagnosis should be considered.

Surgery

If there is visually significant stromal scarring, a penetrating keratoplasty may be performed once the disease is quiescent. Depending on the location and size of the scar, a lamellar keratoplasty may also be used to clear the visual axis. Of note, in eyes that are unable to sustain a clear graft, a Boston keratoprosthesis may be a viable option.

Surgical follow up

Follow-up should be performed as standard of practice for penetrating keratoplasty. Special attention should be paid to signs of recurrence of herpetic disease. Oral antiviral therapy may improve rate of graft survival by decreasing number of recurrences.

Complications

Corneal complications of herpetic eye disease range from epitheliopathy to frank neurotrophic or metaherpetic ulcers. Long standing disciform keratitis may also result in bullous keratopathy. Late complications of deep vascular stromal scarring include secondary lipid keratopathy. Finally, stromal inflammation may lead to visually significant corneal scarring and irregular astigmatism.

Prognosis

Prognosis is usually good, but greatly varies depending on severity and number of recurrences of the disease.

Additional Resources

Region Specific Information (from the AAO's Global Ophthalmology Guide):

- Asia Pacific
- Europe
- Latin America
- Middle East / North Africa

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