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Herpetic Keratitis, Patience is a Virtue: HSK in Immunocompromised Patient

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Herpetic Keratitis, Patience is a Virtue: HSK in Immunocompromised Patient

Abstract

Background: The Herpes virus is ubiquitous in our patient population. Often it is present without symptoms, however, it may present with pain, irritation, and decreased vision. In high-risk populations a longer course of treatment is often required.

Case Report: This case report will detail the treatment options and outcome in a patient with herpes keratitis who also is HIV positive and addresses concerns about treating immunocompromised patients.

Conclusion: This case serves as a review of common and uncommon treatment options for herpes keratitis as well as a review of potential causes of this presentation. Herpetic keratitis is likely to be something most providers will encounter during their careers. Use of oral antivirals is often more cost effect, better tolerated, and improves compliance.

Keywords

Herpes, HSV-1, Viral Keratitis, HIV, Immunocompromised, Corneal Dendrites, Necrotizing keratitis, Geographic epithelial ulcer, disciform keratitis, Herpersiridae

Cover Page Footnote

The author would like to thank his family as this would not have been possible without their support.

INTRODUCTION

Herpes simplex keratitis (HSK) presents after a patient has been exposed to outside viral particles or after reactivation of the herpes simplex virus type 1 (HSV-1) in their cornea. The cornea may respond differently depending on the anatomical location involved.[1]Pertinent terminology may vary widely from one practitioner to another[2] and thus often results in inconsistent diagnosis and treatment from one provider to another. The condition typically presents in otherwise healthy individuals due to the almost ubiquitous presence of the virus within patients as they age. [1,3,4]

CASE REPORT

A 39-year-old African American male presented April 17, 2018 with complaints of redness, photophobia, and decrease in vision in his left eye for about one week. The patient reported being hospitalized for an unknown infection the previous week. Systemic history review revealed a positive history of HIV that was being treated with Norvir® (generic: ritonavir), Prezista® (generic: darunavir), and Tivicay® (generic: dolutegravir) that he was taking with good compliance. These medications are a part of the oft noted "HAART" therapy. While he did not recall his most recent CD4 he thought it was "above 1600" and that his viral load was undetectable at his last examination. He noted an allergy to azithromycin. A further review of systems revealed that he had recently felt fatigued and that he has asthma. The patient noted a history of redness in both eyes that occurred intermittently and usually only lasted a day or two and resolved without the need for intervention. He denied needing glasses. The patient was oriented to time, place, and person.

His distance vision upon initial examination was OD: 20/200 and OS: 20/25. The use of a pinhole did not improve his vision in the right eye. His pupils were round and reactive to light and accommodation. Extra ocular motilities (EOM) had full range of motion in both eyes without pain or diplopia. Confrontation visual fields (CFV) were full to finger counting in both eyes. Intraocular pressures were 11 mm Hg in the right eye and 15 mm Hg in the left eye with a Tonopen at 10:11a m.. Anterior segment examination revealed 2+ injection on the right bulbar conjunctiva, and trace injection on the left bulbar conjunctiva. The adnexa was unremarkable with normal lids and lashes OU; the cornea in the right eye took stain (Figure 1) and the left eye was negative for staining; irises were brown OU, anterior chamber was without cells or flare, angles were open by Van Herick (4/4 OU), and lenses were clear OU.

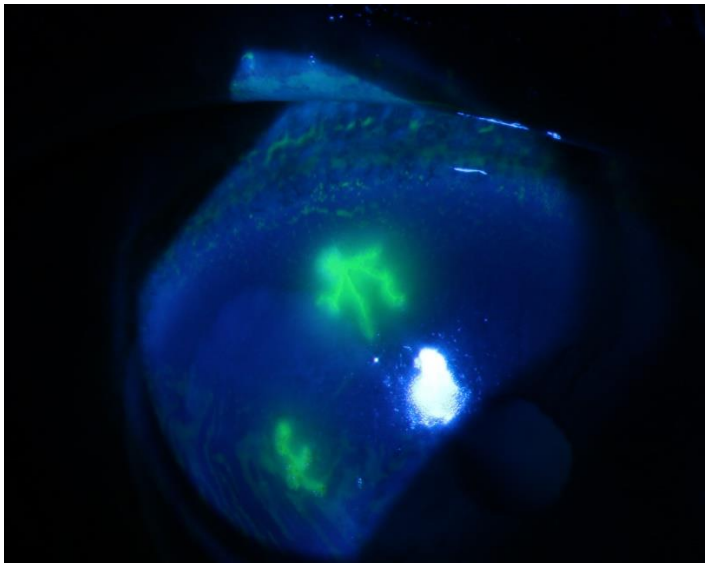


Figure 1. The differential diagnoses considered in this case include:[2]

- Corneal abrasions can be present in patients of any age. However, they often occur as a result of trauma or at least mechanical manipulation of the eye. They are painful and can resolve either following intervention or without it.
- Recurrent corneal erosions occur after an initial corneal insult. They typically occur upon awakening and will recur on an often infrequent and inconsistent time schedule. They occur as a result of damage to the corneal epithelium or epithelial basement membrane.
- Vaccinia keratitis can occur following an inoculation or exposure to smallpox. Vaccinia can be shed from the location of exposure and can be spread by contact to the eye or periocular region.
- *Acanthamoeba* keratitis is considered when the pain is disproportionate to the patient's ocular appearance (high pain with minimal findings). Early in the disease process pseudodendrites can appear on the cornea.
- Bacterial keratitis can result from ocular exposure to one of many bacteria most commonly *Staphylococcus*, *Streptococcus* or *Pseudomonas*. Frequently this presents with concurrent mucopurulent discharge and anterior chamber reaction.
- Herpes Zoster keratitis can present with corneal pseudodendrites (Figure 2), however the keratitis typically presents *following* the presentation of a skin rash. The timing of the presentation can vary in immunocompromised patients. In the past, presentation of HZO in

patients less than 40 years of age was thought to be a potential signifier of HIV.

- Herpes Simplex keratitis presents as a reactivation of the human herpes virus type-1 and is thought to be brought on by fever, stress, trauma, or ultraviolet light exposure. If keratitis is present, it is represented by "true" dendrites with positive stain.

The patient denied any known insult, traumatic or mechanical. While having experienced infrequent bouts of red eye in the past, each had resolved within a couple of days. The patient denied any known exposure to smallpox or its vaccine. His presentation revealed no mucopurulent discharge. This left *Acanthamoeba,* Herpes Zoster, and Herpes Simplex as potential causes. There were no skin lesions present however as indicated above, the keratitis can occur prior to dermatomal rash. The stained corneal lesions were consistent with presentation of true dendrites and thus a diagnosis of Herpes Simplex Keratitis was given. When distinguishing true dendrites from pseudodendrites, one must focus on the presence or absence of "terminal bulbs," widenings at the end of the lesion. Additionally, it is helpful to look for ulceration of dendrites.

The patient was started on oral acyclovir 400 mg 5x/day and trifluridine 9x/day while awake. The patient was educated to the diagnosis and its prognosis (good). The patient was unable to obtain the trifluridine from the pharmacy as it was not in stock. It was stressed that he continue the oral acyclovir and RTC 4 in days for reexamination.

FOLLOW UP #1

The patient did not attend the initially scheduled follow up due to transportation difficulty. He instead returned one week from the initial visit. Upon presentation on April 24, 2018, he denied any change in his medical history. He noted some improvement in the vision in his right eye but denied much improvement in photophobia and irritation. His distance vision in the right eye had improved from 20/200 to 20/60. His pupils, confrontation visual fields and extra ocular motilities were all unchanged and normal OU. His intraocular pressures were 10 mm Hg and 12 mm Hg via Goldmann applanation tonometry at 10:30 am. His right eye still had 2+ injection. The corneal dendrites showed no significant change in appearance. Upon follow up questioning the patient admitted to poor compliance with the oral acyclovir due to the frequency of dosing necessary. The dilated exam revealed no posterior segment involvement. He had clear vitreous OU; cup to disc ratio of 0.25r with sharp margins OU; flat macula OU; normal vessels and no holes or tears in

the periphery in both eyes. His medication was changed to oral valacyclovir 500 mg 2x/day. Due to the patient's complaint of mildly worse pain, a prescription of homatropine 5.0% BID, OD was added. Additionally, gentle corneal debridement of the infected epithelium was performed with fair success. Much of one dendrite was successfully removed while only some of the second dendrite could be removed. Due to the lack of improvement and the initiation of active intervention in office, the follow up was set for 3 days for the patient to be able to be seen prior to the weekend.

FOLLOW UP #2

The patient followed up on April 26, 2018, and once again denied any changes in his medical history. He noted an improvement in vision as well as a reduction of photophobia despite not filling the homatropine prescription. The patient noted that the cost of the medication was too high. The pupils, EOMs and CVF were all unchanged. His vision had improved to 20/40+1 upon examination. The conjunctival injection had improved from 2+ to 1+ at this visit. The dendrites had gotten smaller but were still present. The importance of the oral valcyclovir was stressed and the patient was scheduled for a follow up visit 4 days later.

FOLLOW UP #3

The patient made his final follow up on May 10th (after initially missing the scheduled follow up). He had finished the course of valcyclovir and noted that his vision had returned to normal. The pupils, EOMs and CVFs were all stable. His vision had improved to 20/25. The conjunctival injection had improved from 1+ to trace injection. The dendrites had resolved with only trace superficial punctate keratitis present. The patient was presented with the option of continuing preventative treatment but declined noting the "I probably wouldn't last a week without forgetting." The patient was educated to follow up in 1 year or as needed.

Discussion

A subset of the *Herpesviridae* family *Alphaherpesvirinae* includes: Herpes Simplex type 1 (HSV-1), Herpes Simplex Type 2 (HSV-2), and Herpes Varicella Zoster (VZV) which are most pertinent for this discussion.[3]All three are double stranded DNA.[3] Present throughout the world, and with humans as the only known natural reservoir, herpes is a virus faced by all humanity. Studies have shown that greater than 90% of the world's population test positive for the presence of HSV-1 within their trigeminal ganglia by the age of 60 years old. According to the United Nations Economic and social affairs, the population 60+ in 2015 was 901 million

people and is expected to rise to 1.4 billion by the year 2030.[4] We can extrapolate that, by those numbers, 1.26 billion people will test positive for the HSV-1 virus within their trigeminal ganglion by the year 2030. Presence of HSV-1 within the trigeminal ganglion does not necessarily indicate ocular complications. Herpes Simplex Virus type 1 is responsible for oral infections, (commonly seen as "cold sores) and is most frequently spread by oral-to-oral contact. The second virus HSV-2 is spread through sexual contact and can result in genital sores. Although rare, the HSV-1 virus can also cause genital herpes.[4]

Once someone has the virus, its appearance anywhere along the trigeminal dermatome can be triggered by stress, fever, trauma, or ultraviolet exposure.[1-4] Activation of the HSV-1 virus can affect skin/ eyelid, conjunctiva, cornea, anterior chamber, or retina.

Transmission of the virus can occur through mechanical transfer from a localized skin infection during the approximately 10 days it takes for the lesion to resolve. The viral load can also be high enough in the saliva of an asymptomatic person that contact with their saliva may be enough to transfer the virus to another person.[1,4] Additionally, Kaufman et al. revealed that 98% of asymptomatic HSV-infected patients secreted HSV-1 in either their tears or saliva.[9] Of the 50 patients sampled 13/50 (26%) were IgG negative for HSV-1, thus, suggesting that seronegative patients may have HSV present in either the trigeminal and/ or dorsal root ganglia.[4]

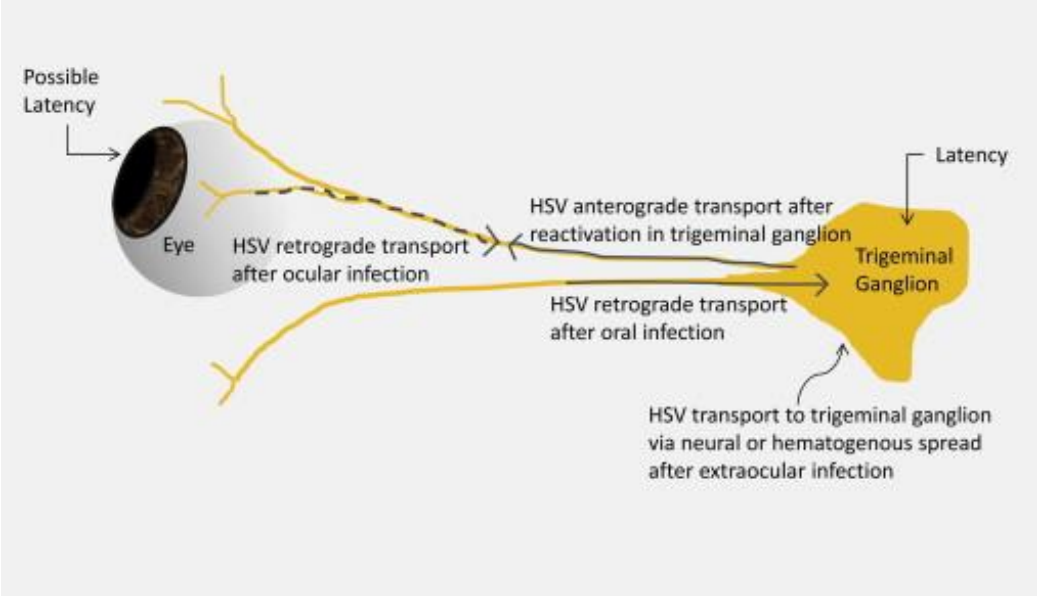
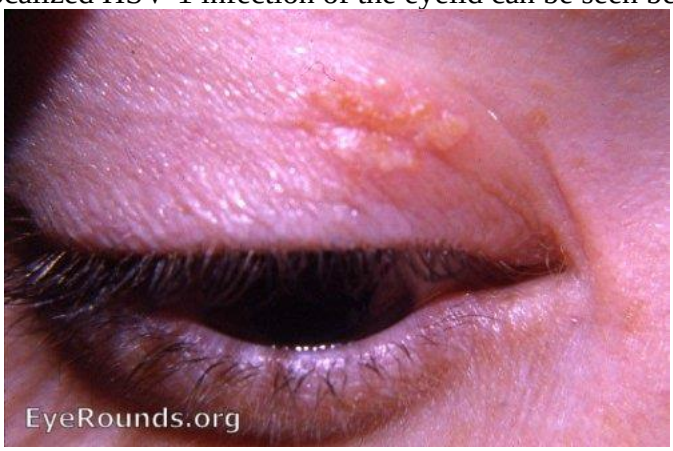


Figure 2.[3] Trigeminal Nerve Pathway

Skin:

A localized HSV-1 infection of the eyelid can be seen below[7]



Here we see small, localized elevations of the skin. They are a group of vesicles with reddening of the tissue deep to them. The lesions have a scalloped border and often have a "crust" due to fluid seepage. They tend to occur and then reoccur in the same area and are typically self-limiting.

Cornea:

There are a variety of terms describing a herpes infection of the cornea. The language used varies from provider to provider and between different disciplines. Table 1 (below) summarizes the location involved as well as terms used to describe it.[4]

Corneal Layer	Nomenclature	Alternate Terms
Epithelium	HSV epithelial keratitis	Dendritic epithelial ulcer Geographic epithelial ulcer
Stroma	HSV stromal keratitis without ulceration	Non-necrotizing keratitis, Interstitial keratitis, Immune stromal keratitis
	HSV stromal keratitis with ulceration	Necrotizing keratitis
Endothelium	HSV endothelial keratitis	Disciform keratitis

TABLE 1. HSV KERATITIS: CLASSIFICATION

The location and extent of the infection is important in determining the proper treatment.

Epithelium:

The corneal epithelium is involved in up to 2/3 of cases that present with ocular involvement. Early lesions appear as superficial punctate keratitis which can form into a dendrite within 12-24 hours. The dendrites form as the infected cell nuclei expand with increasing concentrations of the replicated virus. These cells swell until they burst, releasing high concentrations of the virus to neighboring cells. [1,10]The anatomic effect of the way the virus is passed is what provides "true dendrites" with their classical "terminal bulbs." The terminal bulbs are cells that are swollen with virus that have not yet burst. If the infection continues to spread through the epithelium it can lead to the destruction of the basement membrane. As the basement membrane is responsible for maintaining the bond between the stroma and endothelium, its erosion can lead to the formation of a "geographic ulcer." If the infection occurs near the limbus, the patient may be more symptomatic and may take longer to respond to treatment. Damage to the cornea may result in the patient suffering from recurrent corneal erosions or epithelial granularity. Opportunistic infection may exacerbate the presentation, mandating further treatment. Additionally, the infection may result in the patient having a neurotrophic cornea.

Stroma:

HSV-1 within the stroma causes swelling within the endothelium. It may present either 1) with or without epithelial ulceration. The presence (or lack) of ulceration allows us to decide whether the addition of topical steroids would be helpful. Severe inflammation within the stroma can result in destruction and thinning of the corneal stroma. This inflammation may even result in perforation of the cornea, although that is uncommon unless another bacterial infection is also present. Stromal neovascularization may also occur, and this may present in either a sectoral or diffuse manner.[1]

Endothelium:

Inflammation of the endothelium is much less common than stromal inflammation but may be present. There is difficulty in determining whether the edema present is from a swelling of the stroma or endothelialitis. When endothelial edema is present it tends to appear as a round swelling occupying the central or paracentral cornea. It may be represented via a "ground glass" appearance. A linear endothelitis may appear as a line of keratic precipitate.[1]

Iridocorneal Endothelial Syndrome (ICE):

This condition was originally thought to have been a congenital abnormality however it has been recently considered to be a result of HSV-1. ICE typically presents with unilateral corneal edema, corectopia and presumed trabecular abnormalities. The abnormal trabeculum is responsible for poorly draining the aqueous thus resulting in an elevated intraocular pressure and potentially glaucoma. When this is the case the unilateral corectopia is typically progressive.[1]

Treatment

Treatment involves either oral or topical antivirals. Oral antivirals include acyclovir, valacyclovir and famciclovir; topical medications: trifluridine and ganciclovir. See dosage chart below (Table 2[12]).

Drug (Trade)	Mechanism of Action (MOA)	Dosage
Acyclovir	Interference with viral DNA synthesis	400 mg 5x/day
Valacyclovir (Valtrex)	Prodrug for acyclovir	500 mg TID
Famciclovir (Famvir)	Inhibits DNA chain elongation	250 mg TID
Triflouridine (Viroptic®)	Interference with viral DNA synthesis	Q2H until reepithelization (10-14 days)
Ganciclovir (Zirgan®)	Interference with viral DNA synthesis and Inhibits DNA chain elongation	5x/day until reepithelization, then TID x 1 week

TABLE 2[12] DOSAGE CHART

Treatment can also include mechanical debridement the removal of affected cells would seem to be helpful in reducing the time it takes to the viral concentration to decrease. However, White and Chodosh reveal mixed results with this treatment modality.[4] When applied it should be in concurrence with either topical or oral treatment. Further studies would be helpful in determining whether this helps to improve outcomes.

Immunocompromised

HSV can be an AIDs-defining opportunistic infection although the incidence of HSV keratitis between HIV positive and HIV negative patients is fairly equal.[4] Studies have found mixed results regarding a difference between presentation and duration of treatment when comparing HIV (+) and HIV (-) patients[4]. More research is needed in this area.

Preventative Treatment

The Herpetic Eye Disease Study (HEDs) study (1998) found that there was some success in reducing recurrences of HSV keratitis and HSK stromal disease. In this study, the necessary dosage was 400 mg BID oral acyclovir. This led to a decrease in HSK recurrence of 45% and HSK stromal disease by 42%.[1] However, there is some concern about the usage of acyclovir and a potential for the virus to become resistant.[1,11] While the idea of preventing future occurrences of herpetic eye disease have been proven possible, Lairson et al. have shown in a cost benefit analysis that it would not be cost effective to try to treat every patient with herpetic keratitis with preventive medication. Prophylactic treatment is a valuable tool in the provider's arsenal, but the determination of its applicability should be made on a situational basis.

CONCLUSION

Herpes simplex keratitis can present in varying degrees of severity depending on the individual case. The provider must take care to prescribe medication that can be obtained, and the patient may need to show patience for results, especially if immunocompromised. The use of corneal debridement may be considered on a case-by-case basis but hasn't shown to result in any significant difference in patient outcomes. Additionally, the option of prophylactic treatment should be discussed, but may not be a viable option for every case.

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