Herpes Simplex Keratitis

ABSTRACT

Herpes simplex keratitis is one of the leading causes of infectious corneal blindness in the world. It remains latent in the human host after the primary infection and can be reactivated by many factors. When activated, it travels along the trigeminal nerve to the cornea, and causes recurrent infection which leads to corneal scarring.

Management of the condition is dependent upon the pathogenesis of the disease. Topical antiviral, corneal debridement can be used in the case of herpetic epithelial disease. In the case of herpetic stromal keratitis due to the immune component, topical steroids and antivirals are used to control the condition.

This report describes a case of herpes simplex keratitis that is possibly triggered by surgical trauma.
INTRODUCTION

Herpes simplex keratitis (HSK) is a leading cause of corneal opacification and infection-related visual loss. Even though an individual may not have had clinically apparent disease, high fever, immune-suppression, and sometimes surgery can reactivate latent herpes\(^1\). Its presentation can be distinctively divided into two types, epithelial keratitis or stromal keratitis due to a difference in pathogenesis, this inevitably postulate treatment difference.

In this report, a case of postoperative herpes simplex virus (HSV) keratitis after a cataract surgery is described. The diagnosis and medical management of herpes simplex keratitis are discussed.

CASE REPORT

A 66 year old white male presented with sore, red and weepy right eye 2 weeks post cataract surgery. The patient also complained of foreign body sensation and vision decrease on the visit. His uncorrected VA 1 day post surgery was 6/7.5-2. Prior ocular history included left eye cataract surgery 4 months ago. He was in good health, not atopic and not taking any medications.

Vision

<table>
<thead>
<tr>
<th>OD Vision</th>
<th>OS Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/10-1</td>
<td>6/6-2</td>
</tr>
</tbody>
</table>

Visual acuity

<table>
<thead>
<tr>
<th>OD Vision</th>
<th>OS Vision</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.75/-0.75x86</td>
<td>+0.50/-0.50x86</td>
<td>6/10-1/6/6-2</td>
</tr>
</tbody>
</table>

Slit lamp examination

OD: Dendritic epithelial corneal ulcer inferior central, grade 1 corneal oedema. Anterior chamber grade 2 cells.

OS: Old temporal corneal scar due to previous cataract surgery. No active corneal or anterior chamber inflammation.

Fundus examination

Not performed on presentation.

Diagnosis

Based on the signs and symptoms, the patient was diagnosed with herpes simplex keratitis.
Differential diagnosis

**Epidemic Keratoconjunctivitis (EKC)** Although both condition shares similar ocular signs such as follicular conjunctivitis, lymphadenopathy, and corneal changes, primary herpes simplex keratitis tend to be unilateral while epidemic keratoconjunctivitis are more likely to become bilateral. Given the absence of symptoms and signs in the unaffected eye and the lack of history of contacting with anyone with similar symptoms, this case was therefore not consistent with a diagnosis of EKC.

**Acanthamoeba Keratitis** is associated with a painful red eye with reduced visual acuity. Clinical signs include lid edema, conjunctival injection and dentritiform keratitis. However in this case the patient was not a contact lens wear and was not exposed to any other risk factors such as contaminated water or vegetative matter.

**Herpes Zoster Ophthalmicus (HZO)** The patient in this case did not report experiencing any influenza like illness and no signs of forehead rash or cutaneous vesicle formation were noted. The difference between HZO and HSK also lies between the differences in dendritic lesion appearance, while HSK lesions are larger and has more branching with terminal bulbs, HZO lesions does not.

**Thygeson’s Superficial Punctate Keratitis** is a chronic epithelial keratitis, its onset of symptoms is usually insidious which was not consistent with the acute onset of symptoms in this case. Also no presentation of multiple raised intraepithelial lesions was seen in this patient.

**Recurrent Corneal Erosion (RCE)** is associated with a painful eye on awakening involving epithelial defects. The condition may occur after superficial trauma to the corneal epithelium, due to anterior basement membrane dystrophy or idiopathic. In this case patient presented with sore and red eyes for the past few days without any improvement as opposed to the usual rapid self healing process of RCE. Also common signs such as poor epithelium attachment and epithelial microcysts of recurrent corneal erosion were absent.

**Corneal Abrasion** is associated with history of recent ocular trauma, in this case the lack of such history has ruled out the possibility of corneal abrasion.

Management

This patient was treated with acyclovir eye ointment (3%) five times a day. A review appointment was scheduled in 5 days time.

08/12/2008

Patient best corrected visual acuity was reduced to 6/12-1, corneal oedema remained grade 1, anterior chamber remained grade 2 cells, mild improvement on dendritic ulcer appearance, fine keratic precipitates was present but less ocular redness was noted. Patient
was advised to continue with the same treatment and a further review was scheduled for 4 days later.

12/12/2008

Patient symptoms were reduced. Best corrected visual acuity was improved to 6/7.5-1. Dendritic corneal ulcer was healed, no keratic precipitates was present, anterior chamber cells was decreased to grade 1. A further review was schedule for 1 month later, patient was to continue with the same treatment until next appointment.

**DISCUSSION**

It is understood that currently no treatment has been proven to remove the virus from the ganglia, therefore the goals of treatments are to interfere with viral replication to control virus multiplication, to reduce the recurrence rate and corneal scarring in order to preserve visual acuity and corneal sensitivity. Treatment of HSK is based on whether the condition is caused solely by active virus or if it is due to an immunological reaction to viral antigens in the stroma or endothelium. It is thought the severity of HSK disease is dependent on both virus strains and host factors.

In the case of herpetic epithelial keratitis, the corneal epithelial disease is effectively controlled by topical antiviral agents, clinical trials showed that trifluridine and acyclovir were equipotent in treating the condition, approximately 97% of patients with dendritic ulcer treated with topical trifluridine healed within 2 weeks. Other studies showed that ganciclovir 0.15% gel heals herpès simplex dendritic ulcers as effectively and rapidly as acyclovir 3%ointment but with less effect on vision blurring. As antiviral may cause local toxicity to the corneal epithelium, the dosage frequency can be reduced as the dendritic ulcer begins to heal but should be continued for several days after healing to allow the shedding of dormant virus. In the case of possible drug adverse effects to the corneal epithelium, the use of oral valaciclovir has been reported as a safe and effective alternative to topical antiviral agents. Corneal debridement in adjunction with antiviral agent may accelerate epithelial healing.

Cycloplegic agent may be used (e.g. 5% homatropine twice daily) if anterior chamber reaction is present.

The pathogenesis of herpetic stromal keratitis may involve both immunological and viral component. Cell-mediated immunity in the form of CD4+ T helper lymphocytes and CD8+ cytotoxic T lymphocytes (antigen-specific for viral HSV-1) are generated during a primary corneal infection, these cells persist in patients as long-lived memory and will initiate rapid response to viral reactivation. It is thought that in herpetic stromal keratitis, a chronic low level viral infection of corneal stromal keratocytes exists in the affected area, this provide a chronic stimulus to the antigen-specific T lymphocytes which recognize viral antigens on the keratocytes and kill by a cytotoxic mechanism.
If the herpetic lesion is minimal in herpetic stromal keratitis and the affected individual is immunocompetent then cycloplegic (e.g. 5% homatropine) can be used to control uveitis and ocular lubricants can be offered for symptomatic relief. However if the condition is severe and causes vision disturbance then topical corticosteroids are administered to control inflammation. A study by Wilhelmus et al has shown that topical corticosteroid used in conjunction with antiviral agents reduced the risk of persistent or progressive stromal kerato-uveitis by 68%, and the duration of herpes simplex stromal keratitis was shortened. Due to the active viral component in herpetic stromal keratitis, topical antiviral agent should always be used concurrently with corticosteroids, and the lowest dose of topical steroid that will control the inflammation should be administered. It is best to first start with antiviral therapy to observe the treatment effect prior to the use of corticosteroids as it was shown that postponing steroids use had no detrimental effect on visual outcome at 6 months.

Usually corticosteroids are given four or five times a day and antiviral agent are used at the same frequency, the steroid must be tapered slowly once condition improves and topical antiviral agent can be discontinued when steroids are used less than once a day. Reinstitution of corticosteroid-antiviral therapy may be required if the condition recurs. It is worth to note that patient with previous history herpetic epithelial keratitis and of certain ethnicity (non-white patients) is associated with a higher rate of recurrent epithelial keratitis during the acute treatment of HSV stromal kerato-uveitis hence they should be followed more closely during the treatment.

Necrotizing stromal keratitis is the most severe and prolonged type of keratitis, it is treated with the combination of topical antiviral and corticosteroids, however its response to the treatment is not as responsive as with the disciform keratitis. Penetrating keratoplasty may be performed to replace the scarred cornea with a normal cornea.

The possibility of steroid-induced ocular hypertension should be kept in mind with long term steroid use. The need for supplemental anti-glaucoma medications may need to be considered to control this complication. Suggested options include α-agonist, and carbonic anhydrase inhibitors. Prostaglandins, prostamides, and β-blockers have been implicated in the reactivation of ocular HSV disease, but this has not been proven in scientific studies. A pilot study conducted by Heiligenhaus et al suggested that topical cyclosporin A may be a candidate for the treatment of non-necrotizing stromal keratitis. This is particular helpful in patients who are likely to be steroid responders. A recent study has shown that cyclosporin A can be used to treat patients who are unresponsive to topical prednisolone treatment.

Aside from corticosteroids induced ocular hypertension and glaucoma, HSV itself is also capable of causing kerato-uveitis and secondary glaucoma, this is related to trabecular blockade or trabeculitis caused by the inflammatory aspects of the disease. Hence patient with recurrent herpetic kerato-uveitis should be monitored closely for such complication.

Recurrences of ocular herpetic disease could lead to severe corneal scarring and cause vision loss. The use of oral antiviral for the treatment of herpetic eye disease has been the interest of Herpetic Eye Disease Study (HEDS) group. It was found that low dose oral acyclovir resulted in a 45 percent decrease in the rate of recurrence of ocular HSV disease as
compared with placebo for patients with a history of HSV stromal keratitis\(^\text{17}\). However the prophylaxis effect is less clear for patients who have had only superficial forms of ocular HSV disease\(^\text{17}\). The epithelial keratitis trial also showed no apparent benefit of a 3 week course of oral acyclovir in preventing stromal keratitis or iritis for patient with herpetic epithelial keratitis\(^\text{18}\). The efficacy of oral acyclovir in treating stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine was also investigated, unfortunately oral acyclovir does not appear to be clinically beneficial in this case\(^\text{19}\).

The HEDS group also investigated the association between herpetic keratitis recurrence rate and certain predictor factors. They found that previous epithelial keratitis was not a risk factor for recurrent epithelial keratitis whereas a history of previous stromal keratitis markedly increased the probability of subsequent stromal keratitis\(^\text{10}\). Age, gender, ethnicity and a history of non-ocular HSV infection were not associated with recurrences, and seasonal effects were also not observed\(^\text{10}\).

While current treatment options are effective in stopping virus multiplication or suppressing immune response to viral antigens, the development of vaccine that may block HSV reactivation\(^\text{20}\) or agents that may be used to inhibit the cellular gene pathway responsible for recurrences of viral disease\(^\text{1}\) had been suggested.

Postoperative herpes simplex virus keratitis has been reported in the literature after cataract surgery\(^\text{21,22}\). Although no discrete factors have been identified as triggers for HSV activation, it is suggested that dormant HSV in the trigeminal ganglia might be reactivated by the surgical trauma to the corneal sub-epithelial nerve plexus, and the topical corticosteroids used in the postoperative period may act as an additional stimulus\(^\text{21,22}\). Therefore, patients with a history of ocular or non-ocular HSV disease may require systemic antiviral therapy before and after the procedure as a prophylactic measure, the use of topical non-steroidal anti-inflammatory drugs may be required to treat postoperative inflammation\(^\text{22}\). Although the patient in this case report elicited no such history, the possibility of the uncommon occurrence of HSV keratitis post cataract operation and the management of such complication should be discussed prior to the procedure.

In conclusion, herpes simplex virus establishes its latency in human body after the primary infection and its reactivation is triggered by UV exposure, surgical trauma, stress, immune-suppression, high fever and menstruation\(^8\). Recurrent herpetic episodes are a major cause of corneal scarring and visual loss. Therefore appropriate treatment option is vital in the management of the disease. While topical antivirals remain to be the mainstay of treatment for herpetic epithelial keratitis, the combination of both topical antivirals and topical steroids are used for herpetic stromal keratitis. Prophylactic treatment with oral acyclovir should be considered for patient with a history of stromal keratitis to reduce recurrence rate.
REFERENCES


