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NEGLECTED BILATERAL HERPETIC STROMAL KERATITIS: A CASE REPORT

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ABSTRACT
Herpes simplex virus (HSV) is a DNA virus with a common predilection of mouth, genitalia and eye. HSK can be classified as either necrotizing or non-necrotizing. HSK is primarily diagnosed clinically. It is often treated with a mix of antiviral drugs and local immunosuppressive therapy. The aim is to minimize local symptoms, inflammation, and scar formation.Case description: A 36-year-old female visited the ophthalmology outpatient clinic at Dr. Soetomo General Academic Hospital with a chief complaint of blurry on her both eyes since 8 months ago. She claimed had vesicles in her face and body about 1 years ago. The patient was diagnosed with non necrotizing herpetic stromal keratitis both eyes and complicated cataract in right eye. She had given Acyclovir 400 mg oral; acyclovir 3% eye ointment, prednisolone acetate eye drop,and artificial tears non preservative.Conclusion: Early diagnosis and adequate therapy of HSK are key to avoid complications. Successful treatment reduces disease duration, prevents progressive corneal scaring and reduces risk of further recurrences.

Keywords: herpetic stromal keratitis; herpes simplex virus infection; keratitis

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INTRODUCTION

Herpes simplex virus (HSV) is a DNA virus with a common predilection of mouth, genitalia and eye.1 As many as 3.7 billion people under 50 years old, which is 67% from the global population infected by HSV, according to World Health Organization (WHO).2 Herpetic stromal keratitis (HSK) comprises three major subtypes, namely epithelial, stromal, and endothelial. It develops as a result of an immune response to the virus. Nearly 500.000 people in the USA infected by ocular HSV.1 The incidence of HSK is between 10 to 30 per 100.000 population per year in developed countries and prevalence of 149 per 100.000.3 Herpes simplex virus (HSV) can affect any and all layers of the cornea but recurrent attacks affect more stromal and epithelial layer causing deterioration of vision through corneal scarring and neovascularization. HSK is primarily diagnosed clinically.

A history of repeated herpetic ocular illness and a slit lamp examination of the eye that reveals classic herpetic lesions. PCR analysis and viral culture of the tear film may also show HSV-1 DNA.4Herpetic stromal keratitis (HSK) is often treated with a mix of antiviral drugs and local immunosuppressive therapy. The aim is to minimize local symptoms, inflammation, and scar formation.4 The virus's ability to spread through airborne droplets contributes to its high degree of transmissibility, often leading to blinding corneal ulcers. In addition to the risk of severe vision loss related to HSV keratitis, it impacts quality of life and poses a significant economic burden.5We report the case of neglected herpetic stromal keratitis who presented with blurry vision on both eyes.

CASE DESCRIPTION

A 36-year-old female visited the ophthalmology outpatient clinic at Dr. Soetomo General Academic Hospital with a chief complaint of blurry on her both eyes since 8 months ago. The eyes blurred slowly as if covered in smoke. She initially claimed to have vesicles in her face and body before the eyes started blurry.She also complained pain and discomfort on both eyes.The patient had been treated by an ophthalmologist 7 months ago, given eye drops but the patient forgot the medicine. She said the medication hasn't improved. She was treated again to the ophthalmologist near her residences then referred to Dr. Soetomo General Academic Hospital. Priorly, patients claim to be able see normally. There were neither history of recurrent red eye nor history of pain in the knees or finger. She had vesicles in her body about 1 years ago. There was neither diabetes mellitus nor hypertension. She was given artificial tears eye drop on both eyes. There was no history of the same illness or allergies in the family, trauma, or spectacles.The patient was alert and the vital sign was within normal limit.From ophtalmology examination. The visual acuity both eyes were light perception and have good light perception. intraocular pressure was within normal limit. There were minimal spasm of eyelid, conjunctiva injection with discharge both eyes. There was corneal opacity and stromal edema also stromal neovascularization was found in both eyes.There is no epithelial defect.Fluorescein test was negative in both eyes. Anterior chamber was deep, iris radier, pupil was round , 3 mm in size and there was lens opacity of the right eye.The left eye is difficult to evaluate due to corneal opacity.

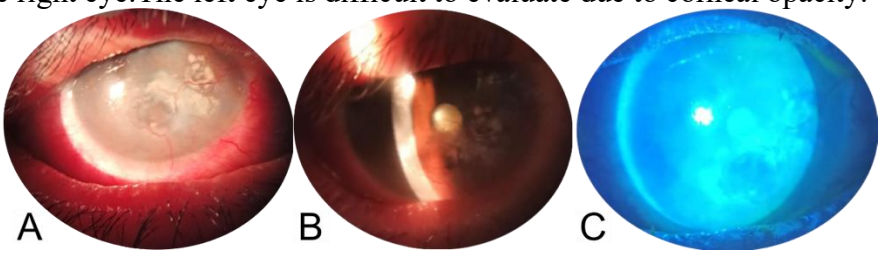


Figure 1. Clinical examination of the right eye. *(Permission of the patient. Courtesy of Dr. Soetomo General Academic Hospital)*

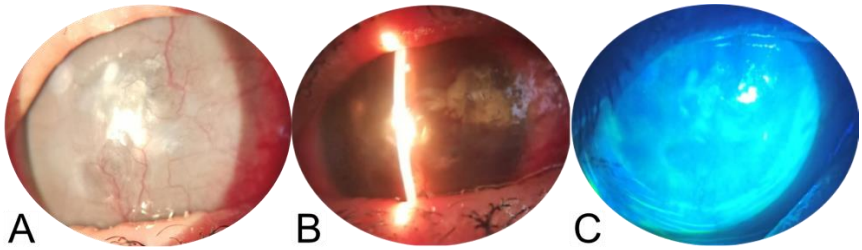
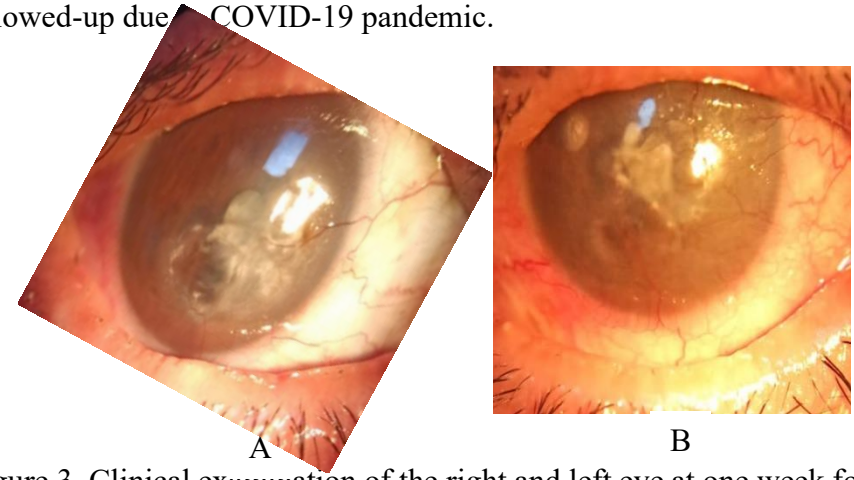


Figure 2. Clinical examination of the left eye. *(Permission of the patient. Courtesy of Dr. Soetomo General Academic Hospital)*

Laboratory examination blood test show normal limit.The patient was diagnosed with non necrotizing herpetic stromal keratitis in both eyes and complicated cataract on right eye. She had given Acyclovir oral 400 mg 5 times daily for 10 days and continue with 400 mg every 12 hours; acyclovir 3% eye ointment every 4 hours both eyes; Natrium Carboxymethylcellulose non preservative eye drop every hours both eyes; and prednisolone acetate eye drop every 4 hours both eyes. The patient came for followed up after one week. The visual acuity both eyes still light perception.There was no spasm of eyelid an injection of conjunctiva was reduce.Improvement of corneal opacity was obtained than before.As we can see in figure 3,there was improvement after on week medication although the persistent neovascularization and corneal opacity are still visible. The patient then continued the oral and topical medication,Acyclovir 400 mg every 12 hours oral; acyclovir 3% eye ointment every 4 hours both eyes; Natrium Carboxymethylcellulose non preservative eye drop every hours both eyes; and

prednisolone acetate eye drop every 4 hours both eyes. The patient was not come for another followed-up due to COVID-19 pandemic.



A B

Figure 3. Clinical examination of the right and left eye at one week followed-up. *(Permission of the patient. Courtesy of Dr. Soetomo General Academic Hospital)*

DISCUSSION

Herpes simplex virus (HSV) is a large double stranded DNA viruses and a member of human α-herpesvirus family.3 It can be divided into HSV-1 and HSV-2. HSV-1 is transmitted via direct contact, usually via saliva. It causes an eye infection and significant visual impairment. After the primary infection, the virus enters nerve cells in the dorsal ganglia and become latent.2 Shrestha et al., found the predilection of HSK was on 47.19±16.69 years old patient, which 28 females and 10 males. Another study stated that the incident was on 29.9±16.69 years old female and 32.09±15.79 years old male.1 Our patient was 36th years old female. Herpes simplex infection (HSV) worse in immunodeficient patient, such as diabetes mellitus, measles infection, organ transplant recipient and acquired immune deficiency syndrome (AIDS).2,6,7 Shrestha et al., stated that, most of the patients, 50% had history of spontaneous onset of disease followed by other triggering factors, namely 26.3%stress, 34.2% fever, 21.05% foreign body, 15.7% skin eruptions and 13.1% UV light.1 A study from Hsu et al., found that overweight and obesity were revealed as risk factors for HSK recurrence in patients receiving long-term antiviral prophylaxis.8 There was no other risk factor for the occurrence of HSK in our patient, beside a vesicles in face and body about 1 years ago as the primary infection.

Neutrophil and CD4+ mediated mechanisms are involved in the pathogenesis of HSK following viral spread along the corneal epithelium.9 In mouse models of recurrent HSK, corneal sensory nerve retraction and replacement with aberrant sympathetic nerves potentiate pathologic processes with CD4+ T cells post-HSV-1 reactivation. Damage at the level of sensory corneal nerves is termed neurotrophic keratopathy. Substance-P (SP) production is largely depleted during the early stage of corneal nerve damage in HSK, followed by increased levels, possibly via a positive feedback loop during corneal disease manifestation; this surge of SP binds to neurokinin-1- receptor, upregulating the release of pro-inflammatory cytokines on the ocular surface.7,10 HSK can be classified as either necrotizing or non-necrotizing.An overlying epithelial defect is frequently observed in necrotizing HSK, and the likelihood of stromal dissolving and perforation is elevated.However, in non-necrotizing HSK, which is also referred to as immune or interstitial HSK, the epithelium remains intact, and the pathology is believed to be primarily driven by the host immune response.14

Necrotizing or non-necrotizing stromal keratitis are part of stromal keratitis due to HSV. Non-necrotizing stromal keratitis presents with corneal stromal oedema and folds in Descemet's membrane. This is associated with fine keratic precipitates (KP),raise intraocular pressure (IOP); there is no epithelial defect. Necrotising stromal keratitis is due to active viral infection within the cornea. It presents with an epithelial defect and dense stromal infiltration. If the infection is close to the limbus, then the marginal keratitis shows stromal infiltration and associated vascularisation.2,11 Our patient diagnosed with non necrotizing herpetic stromal keratitis both eyes because there was stromal edema an there was no epithelial defect found,but there is no raise of IOP.Long- standing HSV interstitial keratitis can be associated with corneal vascularization.Symptoms of herpes simplex keratitis are redness, discharge, watery eyes, irritations, itching, pain and photophobia.6,12 Decrease vision in keratitis is usually due to the involvement of stroma and endothelium. A study from Shrestha et al., found as many as 13.15% had a 6/6– 6/18, 31.5% had a vision of 6/24–6/60, 34.21% less than 6/60–3/60, and 21.05% <3/60.1 Stromal haze/opacity without ulceration, lipid keratopathy, oedema, scarring, sectoral of diffuse neovascularisation, corneal thinning, and immune ring can be found in stromal HSK.6

Herpetic stromal keratitis (HSK) may be diagnosed by its clinical presentation on the slit-lamp biomicroscope. Active HSK on OCT shows significant epithelial and stromal thickening while the inactive disease process shows a change in the structure at the site of stromal thinning due to the scarring.7,10 Our patient diagnosed with non necrotizing herpetic stromal keratitis both eyes. The diagnosis was made by history of the patient and clinical examination of our patient.The virus can be detected in a corneal scrap using cell culture, indirect immunofluorescence (IFA) or PCR for detection. Secondary bacterial infection should be excluded.2,3 HSV DNA PCR has sensitivity of 100%. The gold standard for HSK diagnosis is virus culture, it has 100% specificity but low sensitivity. Immunohistochemistry's specificity is poorer than for PCR but sensitivity is as high as 80%. The absence of IgG and IgM HSV-specific antibodies however can be helpful in excluding HSK. Individuals typically remain seropositive once infected with seroreversion rates of 1% and 5% over 15 years for HSV-1 and 2, respectively.3

Treatment of primary herpes infection is controversial as it is often self-limiting. Topical and systemic antivirals have been used.2 The preferred treatment for HSV stromal keratitis is an oral antiviral agent combined with a topical corticosteroid, the latter tapered over a period greater than 10 weeks. Stromal keratitis with intact epithelium can be treated with pro-phylactic doses of antiviral medication, whereas ulcerating disease often requires therapeutic doses from its early stages.12 Our patient was giver acyclovir oral and steroid eye drop Acyclovir is a prodrug that, once entering the host cell, is phosphorylated by the HSV protein thymidine kinase (TK), before being twice more phosphorylated by host enzymes to its active form acyclovir triphosphate. Acyclovir is available as an oral, intravenous and topical formulation.13 Acyclovir has good oral bioavailability although absorption decreases with increasing dose, namely 20% of 200 mg and 12% of 800 mg due to absorption saturation; intravenous compared to oral Acyclovir has around eight times higher bioavailability.3 Acyclovir eye ointment 3% five times/day for 7 days, and then three times daily for a further 7 days is recommended for dendritic ulcers.2 Acyclovir has weaknesses, namely viral drug resistance, particularly in immunocompromised patients, block viral replication they are not directly active against viral proteins, and not effective in elimination of latent infection.3

Despite the significant benefit in the steroid-treated group, it was found in this group that half of the failures occurred within 6 weeks of completing steroid treatment.3 Among the current local therapy options, local steroid eye drops are known to decrease neutrophil chemotaxis

and thereby diminish the collagenase and cytokine load, which leads to ulceration and eventually scarring development. Side effects of topical corticosteroids include the probable return of herpetic illness, increased intraocular pressure (IOP), the development of glaucoma, and cataract formation. Furthermore, despite the use of topical corticosteroids, some individuals experience prolonged inflammation.4,12 Cataracts in this patient form as a result of an inflammatory process that is not properly managedNon-Necrotizing stromal keratitis is managed with topical low-dose corticosteroids 4–6 times/day with gradual tapering for 4–6 weeks, along with either topical acyclovir ointment 5 times/day or topical trifluridine for 2–3 weeks. For recurrent cases, provide prophylactic cover by giving oral acyclovir 200–400 mg 2 times/day.2,12 Our patient was given acyclovir 400 mg oral and acyclovir 3% eye ointment and prednisolone acetate eye drop also artificial tears for lubrication.

Herpetic keratitis leads to cornea ulcer and corneal perforation and neurotrophic keratitis. HSK may also be a causative factor of corneal graft failure. Retrograde inflammation from the cornea to the anterior chamber can result in viral anterior uveitis. HSV may also lead to uveitis. Posterior uveitis has been postulated to occur following long periods of post-keratitis latency. Besides that, cornea denervation can be found.7

CONCLUSION

Herpetic virus keratitis is the cause of blindness worldwide. Early diagnosis and adequate therapy are key to avoid complications. In HSK, the diagnosis is mainly based on clinical examination. PCR testing can also be used; however, it is not useful in stromal and endothelial HSK due to their immune-related pathogenesis. Successful treatment reduces disease duration, prevents progressive corneal scaring and reduces risk of further recurrences.

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