

HERPES SIMPLEX UVEITIS
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In November of 1992, a 55 years old lady presented with:

PRESENTING COMPLAINT

Blurry vision and mildly red and moderately photophobic OD for the past 5 days.

HISTORY of presenting complaint

In June, 1990, a flare up of Iritis OD with increased IOP. Treated with diuretics and topical steroids and miotics. She was on maxidex, cyclogyl, dolobid and artificial tears on the day of presentation. She was also on estrogen and provera.

PAST OCULAR HISTORY

She had a history of iritis OD, for the past 25 years, which would intermittently flare up, treated with topical steroids and cycloplegics. She had had facial herpetic dermatitis earlier. Her raised IOP was attributed to steroid use and responded well to a decrease in dose of the same. Her iritis was kept at bay only to flare up at the lowest dose of topical medication.

PAST MEDICAL HISTORY

- Hypertension
- Pneumonia
- Mitral valve prolapse
- Sinus problems
- Stiff lower back
- Muscle aches

ALLERGIES

- Hay fever
- Scopolamine

FAMILY HISTORY

- CAD
- Diabetes Mellitus type 2
- Glaucoma
- Cataracts

EXAMINATION

	CC	PH	A
VISION			
OD	20/30	NI	17
OS	20/25	NI	15

- *Corneal Sensation* was decreased in the right eye.

SLIT LAMP EXAMINATION		
	OD	OS
Lids/lashes	-	-
Conjunctiva	Trace redness	-
Sclera	-	-

Cornea	Old KPs	-
Tear Film	Decreased	-
Anterior Chamber	Rare cell	D + Q
Iris	<ul style="list-style-type: none"> • Patchy iris atrophy • Posterior Synechiae 	-
Lens	PSC 2+	clear

FUNDUS EXAM was unremarkable.

ASSESSMENT

HSV Uveitis

PLAN

She was started on Acyclovir 800mg QD.

FOLLOW UP

Her AC was quiet on the 4-wk follow up with no subsequent flare-ups. She has since been on 800mg of Acyclovir.

Doing well.

Discussion

Herpes simplex uveitis is an ocular uveal inflammation secondary to viral infection caused by Herpes simplex virus (HSV). There are over 500,000 episodes of active herpes simplex ocular infection every year in the USA alone, and ocular HSV is one of the leading causes of blindness in developed countries.¹⁻⁵ Ocular infection caused by HSV may involve both ocular anterior and posterior segments that results in various clinical disorders, including blepharitis, conjunctivitis, scleritis, episcleritis, keratitis, anterior uveitis, vitritis and retinitis.^{2,6-8} HSV is one of the most common infectious causes of uveitis, accounting for up to 9% of cases of anterior uveitis in published series.^{4,9} HSV uveitis may occur as an anterior uveitis, posterior uveitis, panuveitis, keratouveitis, and sclerokeratouveitis. The inflammatory reaction can present as an acute, chronic or recurrent course. Acute HSV uveitis is frequently associated with corneal involvement causing keratitis, however uveitis caused by HSV can also occur without corneal inflammation.

Epidemiology

The incidence of HSV uveitis is established at onset of uveitis in only 4% to 9% of cases, and can increase to as high as 44% after a long period of follow-up in some series.^{4,5,9} HSV uveitis usually occurs in middle age, with a mean age at onset of clinical diagnosis around 41 to 46.3 years old.^{4,5} The average time interval between the onset of ocular disease and diagnosis is 3.4 years. There is no sexual predilection and both genders may be affected with equal frequency.⁵ HSV uveitis has a high missed or ignored diagnostic rate (70% of 41 patients) reported in one series.^{4,5} A delayed diagnosis may occur for years (average >3 years) between first presentation to an ophthalmologist and eventual diagnosis of the herpetic etiology.⁴

Clinical Characteristics

HSV infection involving the uveal tract usually presents as an anterior uveitis or iridocyclitis (85% of cases reported in one study),⁵ although posterior uveitis, panuveitis or retinitis (acute retinal necrosis) may also occur (about 15% cases).^{5,10-12} Clinical symptoms and signs of an anterior uveitis caused by HSV may include unexplained corneal scarring, decreased corneal sensation (50% of patients), focal or diffuse patchy iris atrophy, iris transillumination defects, anterior and/or vitreous cells, granulomatous or non-granulomatous KPs, posterior iris synechiae, and elevated intraocular pressure. Inflammation involving the posterior segment may result in cystoid macular edema, retinal vasculitis, papillitis, and spontaneous hyphema, even acute retinal necrosis. Another common and important characteristic of HSV uveitis is that it usually presents as a unilateral recurrent inflammation. It has been reported that about 85% of patients with HSV uveitis usually present as a unilateral involvement of ocular inflammation, and only 8% of patients have bilateral uveitis.⁵ In addition, HSV uveitis is often associated with corneal involvement, with HSV keratitis; only about 15% patients may present ocular inflammation without corneal involvement.^{4,5}

PATHOGENESIS

The pathogenesis of HSV uveitis, although not completely understood, is believed to include

various mechanisms such as viral replication, ischemic vasculitis, lymphocytic infiltration of the iris stroma or intraocular nerves.^{5,12-16} In addition, persistent and recurrent viral infection may cause an inflammatory reaction manifested as uveitis, or can trigger the immune system itself against viral antigens, eventually causing tissue and organ inflammation and damage.^{4,12}

Diagnosis

The diagnosis of HSV uveitis is made clinically, primarily based on a comprehensive medical and ophthalmologic history as well as a thorough ophthalmologic examination. All ocular inflammatory disorders that present a feature of recurrent unilateral uveitis with characteristic corneal epithelial ulcers or with a past history of keratitis or unexplained corneal scar in the same eye may indicate a herpetic infection and inflammatory course. In the absence of keratitis or corneal scar, the diagnosis is more difficult. However, other symptoms and pathological signs such as unilateral granulomatous or nongranulomatous uveitis associated with sectoral or diffuse patchy iris atrophy, corneal hypoesthesia, iris transillumination, and elevated intraocular pressure, are also important clinical clues that should raise a high suspicion of herpetic uveitis. One clinical study has reported that almost 50% of patients with HSV uveitis exhibit decreased corneal sensation. Therefore, in patients with a suspicion of herpetic uveitis, corneal sensation should be tested, which may provide another clinical diagnostic clue.^{4,9}

Laboratory tests such as polymerase chain reaction (PCR) is a powerful tool for diagnosing herpetic uveitis. It has been reported that PCR can provide 80% to 90% positive diagnosis rate by detecting the presence of HSV DNA in the aqueous humor and in the vitreous in patients with a clinical herpetic infection.^{1,9,17-22} Aqueous is usually harvested by an anterior chamber tap during an episode of active inflammation.⁴ PCR testing is especially suggested and should be considered when the diagnosis is in doubt. Other diagnostic methods such as detecting antibody levels in aqueous has also been used.^{18,20,23-25}

TREATMENT

Topical steroid is usually used as initial treatment in patients with HSV uveitis. Prophylactic oral acyclovir has been widely studied and has shown an effect in preventing recurrence and improving outcome of HSV uveitis, especially with long-term therapy.²⁶⁻³⁵ In Dr. Foster's practice, patients with a history of current herpetic uveitis have been treated with 800 mg of acyclovir once a day for a minimum of 3 years for the past decade. A prolonged prophylactic effect of oral acyclovir in preventing relapses of herpetic uveitis has been confirmed in a randomized, placebo-controlled study carried out by this Service and in other clinical studies. 26-35

COMPLICATION AND

Prognosis

Ocular complications caused by HSV uveitis may include secondary glaucoma, cataract, corneal perforation, epiretinal membrane, retinal detachment and endophthalmitis. Secondary glaucoma is the most common complication in patients with herpetic uveitis.⁵ It has been estimated that 28% to 45% of patients with HSV keratouveitis may develop transient elevated IOP,³⁶ and 10%³⁶ to 54%⁵ of patients with HSV uveitis may present with secondary glaucoma.⁵ Various mechanisms are responsible for elevated intraocular pressure, including trabeculitis, debris and inflammatory cells in the trabecular meshwork, and prolonged use of steroids.^{4,37,38} Treatments of secondary glaucoma include topical anti-glaucoma drugs and surgery.

Cataract is the second most frequent complication, occurring in 20% of patients with HSV uveitis. It can be secondary to intraocular inflammation itself or to steroid therapy.⁵ Cataract extraction is an effective method of treatment.

Corneal perforation, retinal detachment, and endophthalmitis are rare but severe complications associated with HSV keratouveitis.

The prognosis of HSV uveitis varies with the severity and location of the ocular inflammatory involvement, as well as its complications. Severe corneal involvement, inflammation involving the posterior pole, and severe complications such as corneal perforation, retinal detachment, and endophthalmitis obviously bring an unfavorable outcome. Early diagnosis and initiation of treatment, especially with prophylactic oral acyclovir, can prevent recurrences and reduce the prevalence of severe complications.

References

1. Harper SL, Foster CS: Recurrent herpetic uveitis. Abstract book, New England

- Ophthalmologic Society. 1999; pp.18.
2. Liesegang TJ: Epidemiology of ocular herpes simplex: Natural history in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol* 1989;107:1160-1165.
 3. Barron BA, Gee L, Hauck WW, et al: Herpetic Eye Disease Study: a controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994;101:1871-1882.
 4. Waheed NK, Miserocchi E, Baltatzis S, Foster CS: Diagnosis of recurrent herpes simplex uveitis. *Am J Ophthalmol*. In press.
 5. Miserocchi E, Waheed NK, Dios E, et al: Outcome in HSV and VZV uveitis: a clinical evaluation and comparison. In press.
 6. Corey L: Herpesviruses. In Sherris JC, Ryan KG (eds): *Medical Microbiology*. New York: Elsevier, 1984:411-426.
 7. Wilhelmus KR, Gee L, Hauck WW, et al: Herpetic Eye Disease Study: a controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology* 1994;101:1883-1896.
 8. Schacher S, Garweg JG, Russ C, Bohnke M: Diagnosis of herpetic uveitis and keratouveitis. *Klin Monatsbl Augenheilkd* 1998;212:359-362.
 9. Rodriguez A, Power WJ, Neves RA, Foster CS: Recurrence rate of herpetic uveitis in patients on long term oral acyclovir. *Doc. Ophthalmol*. 1995;90:331-40.
 10. Liesegang TJ: Classification of herpes simplex virus keratitis and anterior uveitis. *Cornea* 1999;18:127-42.
 11. Kaufman HE, Barron BA, McDonald MB: *The Cornea*. 2nd edition. Boston: Butterworth-Heinemann, 1998. Chapter 10: Herpes simplex viral infections; Chapter 11: Varicella Zoster viral infection.
 12. Liesegang TJ: Ocular herpes simplex infection: pathogenesis and current therapy. *Mayo Clin Proc* 1988;63:1092.
 13. Sundmacher R and Neumann-Haefelin D: Herpes simplex virus isolations from the aqueous of patients suffering from local iritis, endotheliitis, and prolonged disciform keratitis with glaucoma. *Klin Monatsbl Augenheilkd* 1979;175:488-501.
 14. Pavan-Langston D: Herpes Zoster Ophthalmicus: Medical and surgical management. In Spaeth G, Katz L, Parker KW (eds): *Current therapy in ophthalmic surgery*. Philadelphia: BC Decker, 1989:99.
 15. Liesegang TJ: Corneal complications from herpes zoster ophthalmicus. *Ophthalmology* 1985;92:316-24.
 16. Kijlstra A: The value of laboratory testing in uveitis. *Eye* 1990;4:732-736.
 17. Kowalski RP, Gordon YJ, Romanowski EG, et al: A comparison of enzyme immunoassay and polymerase chain reaction with the clinical examination for diagnosing ocular herpetic disease. *Ophthalmology* 1993;100:530-533.
 18. Foster CS: Herpes simplex virus-induced destructive corneal disease. *Eye* 1989;3:194-203.
 19. de Boer JH, Verhagen C, Bruinenberg M, et al: Serologic and polymerase chain reaction analysis of intraocular fluids in the diagnosis of infectious uveitis. *Am J Ophthalmol* 1996;121:650-658.
 20. Power WJ: Primary varicella-zoster keratitis: diagnosis by polymerase chain reaction. *Am J Ophthalmol* 1997;123:252-254.
 21. Berra A, Dutt JE, Foster CS: Detection of herpes simplex virus type 1 by an in situ polymerase chain reaction technique. *Cornea* 1996;15:55-61.
 22. Baarsma GS, Luyendijk L, Kijlstra A et al: Analysis of local antibody production in the vitreous humor of patients with severe uveitis. *Am J Ophthalmol* 1991;112:147-150.
 23. Kijlstra A, van den Horn GJ, Luyendijk L et al: Laboratory tests in uveitis: new developments in the analysis of local antibody production. *Documenta Ophthalmologica* 1990;75:225-231.
 24. Haut J, Roman S, Morin Y et al: Search for etiology in 110 cases of uveitis. Value of punctures of the aqueous humor and vitreous body. *J Fr Ophtalmol* 1995;18:292-304.
 25. The Herpetic Eye Disease Study Group: Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med* 1998;339:300-6.
 26. Colin J, Malet F, Chastel C: Acyclovir in herpetic anterior uveitis. *Ann Ophthalmol* 1991;23:28-30.
 27. Hoang Xuan T, Bichi ER, Herbort CP et al: Oral acyclovir for herpes zoster ophthalmicus. *Ophthalmology* 1992;99:1062-1071.

28. Tambasco FP, Cohen EJ, Nguyen LH, et al: Oral acyclovir after penetrating keratoplasty for herpes simplex keratitis. *Arch Ophthalmol* 1999;117:445-449.
29. Herbolt CP, Buechi ER, Piguet B, et al: High dose oral acyclovir in acute herpes zoster ophthalmicus: the end of the corticosteroid era. *Curr Eye Res* 1991;10 (suppl.):171-176.
30. Rodriguez A, Power WJ, Neves RA, Foster CS: Long-term systemic acyclovir in the management of the current herpes simplex keratouveitis. *Excerpta Medica, International Congress Series 1068*. pp. 465-468.
31. Foster CS, Barney NP: Systemic acyclovir and penetrating keratoplasty for herpes simplex keratitis. *Doc Ophthalmol* 1992;80:363-9.
32. Barney NP, Foster CS: A prospective randomized trial of oral acyclovir after penetrating keratoplasty for herpes simplex keratitis. *Cornea* 1994;13:232-236.
33. Rodriguez A, Power WJ, Neves RA, Foster CS: Recurrence rate of herpetic uveitis in patients on long-term oral acyclovir. *Doc Ophthalmol* 1995;90:331-340.
34. Falcon MG, Williams HP: Herpes simplex kerato-uveitis and glaucoma. *Trans Ophth Soc U K* 1978;98:101-104.
35. O'Connor GR: Recurrent herpes simplex uveitis in humans. *Surv Ophthalmol* 1976;21:165-70.
36. Karbassi M, Raizman MB, Schuman JS: Herpes zoster ophthalmicus. *Surv Ophthalmol* 1992;36:395-410.

HSV Uveitis and Scleritis

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HSV UVEITIS:

1. All of the following statements regarding HSV uveitis are true except:
 - A. HSV is a common etiologic agent for infectious uveitis
 - B. It can have an acute, chronic or recurrent course.
 - C. Can also occur without corneal involvement
 - D. Can commonly cause bilateral recurrent inflammation

2. Choose a single best answer regarding the clinical symptoms and signs of an anterior uveitis caused by HSV:
 - A. unexplained corneal scarring
 - B. decreased corneal sensation
 - C. granulomatous or non-granulomatous keratic precipitates
 - D. anterior and/or vitreous cells
 - E. All of the above

3. Regarding the strategies utilized in the diagnosis of HSV uveitis mark the following statements as true or false:
 - A. HSV uveitis is usually diagnosed clinically
 - B. Detecting antibody levels in the aqueous is a common diagnostic tool.
 - C. Recurrent unilateral uveitis with characteristic corneal epithelial ulcers or with a past history of keratitis or unexplained corneal scar in the same eye may indicative of and HSV uveitis.
 - D. PCR is a powerful tool in diagnosing herpetic uveitis.

4. The most common ocular complication of HSV uveitis is:

- A. Cataract formation
- B. Secondary glaucoma
- C. Corneal perforation
- D. Retinal detachment

5. Choose a single best answer regarding the possible anatomical presentations of HSV infection involving the uveal tract:

- A. Anterior uveitis or iridocyclitis
- B. Posterior uveitis
- C. Panuveitis
- D. Retinitis/ acute retinal necrosis
- E. All of the above

ANSWERS:

- 1. D
- 2. E
- 3. A-t, B-f, C-t, D-t
- 4. A
- 5. E

HSV SCLERITIS:

A. Which one of the following is a single best choice regarding immune mediated reactions induced with HSV infection of the cornea:

- 1. Necrotizing keratitis
- 2. Interstitial Keratitis
- 3. Nummular keratitis
- 4. Disciform keratitis
- 5. All of the above

B. Regarding the pathogenesis of HSV scleritis mark the following statements as true or false:

- 1. Granulomatous inflammation of the sclera clinically indistinguishable from that occurring in connective tissue disorders.
- 2. Direct HSV invasion during active infection (often associated with epithelial infectious ulceration)
- 3. Often does not involve necrotizing stromal disease.
- 4. Is often associated with necrotizing or interstitial keratitis, immune rings, limbitis, disciform keratitis, PUK

C. Choose a single best answer regarding the differential diagnosis of HSV scleritis:

- 1. Autoimmune scleritis
- 2. Pseudomonas infection
- 3. Syphilis
- 4. Sarcoidosis
- 5. All of the above

D. All of the following steps are useful in the management of HSV scleritis except:

1. Systemic anti-viral therapy
2. Topical prednisolone, NSAID, scopolamine and antibiotic.
3. Surgical management alone
4. Surgical intervention along with medical management may be required

E. Choose a single best answer regarding dilemmas associated with the management of HSV scleritis:

1. Poor penetration of antibiotics in the nearly avascular sclera
2. Ability of microbial organisms to persist in the avascular interscleral lamellae
3. Occurs in immunocompromized hosts
4. Ability of microbial organisms to persist long periods of time without inciting an inflammatory response
5. All of the above

ANSWERS:

A. 5

B. 5.

C. 1-t, 2- t, 3-f, 4-t

D. 3

E. 5