Grand Rounds

Jonathan D. Gambrell, M.D.
University of Louisville School of Medicine
Department of Ophthalmology & Visual Sciences
11/05/2010

Presentation

- CC: evaluation for corneal transplant
- HPI: 54yo white male presents with desire to be evaluated for corneal transplant. He states having waxing/waning visual acuity and foreign body sensation since a concrete mixer exploded near him, getting concrete in his eye in 1991. He states that over the past two months, the foreign body sensation and photosensitivity returned. His visual acuity had decreased as well.

History

- POH: concrete mixer explosion, pool cue chalk in eye
- PMH: COPD
- Family History: glaucoma
- Social history: smokes 2 packs/day
- Medications: Advair, spiriva, fluticasone, occasional oral steroid use
- Allergies: Penicillin

Exam Findings

	OD	**OS**
VA:	20/20	20/250
Pupils:	4 → 3 no RAPD by reverse technique	poor view
IOP:	16	26
EOM:	Full	Full

Exam Findings

	OD	OS
Ext	No swelling, or ecchymoses OU	
L/L	No lid lesions	OU
Conj	wnl	1-2+injection
K	no staining	see description on following slides
AC	no cell or flare	poor view/formed
Iris	wnl	visible portion wnl
Lens	1+NS	no view
Vit	no cells	no view
DFE	wnl	no view

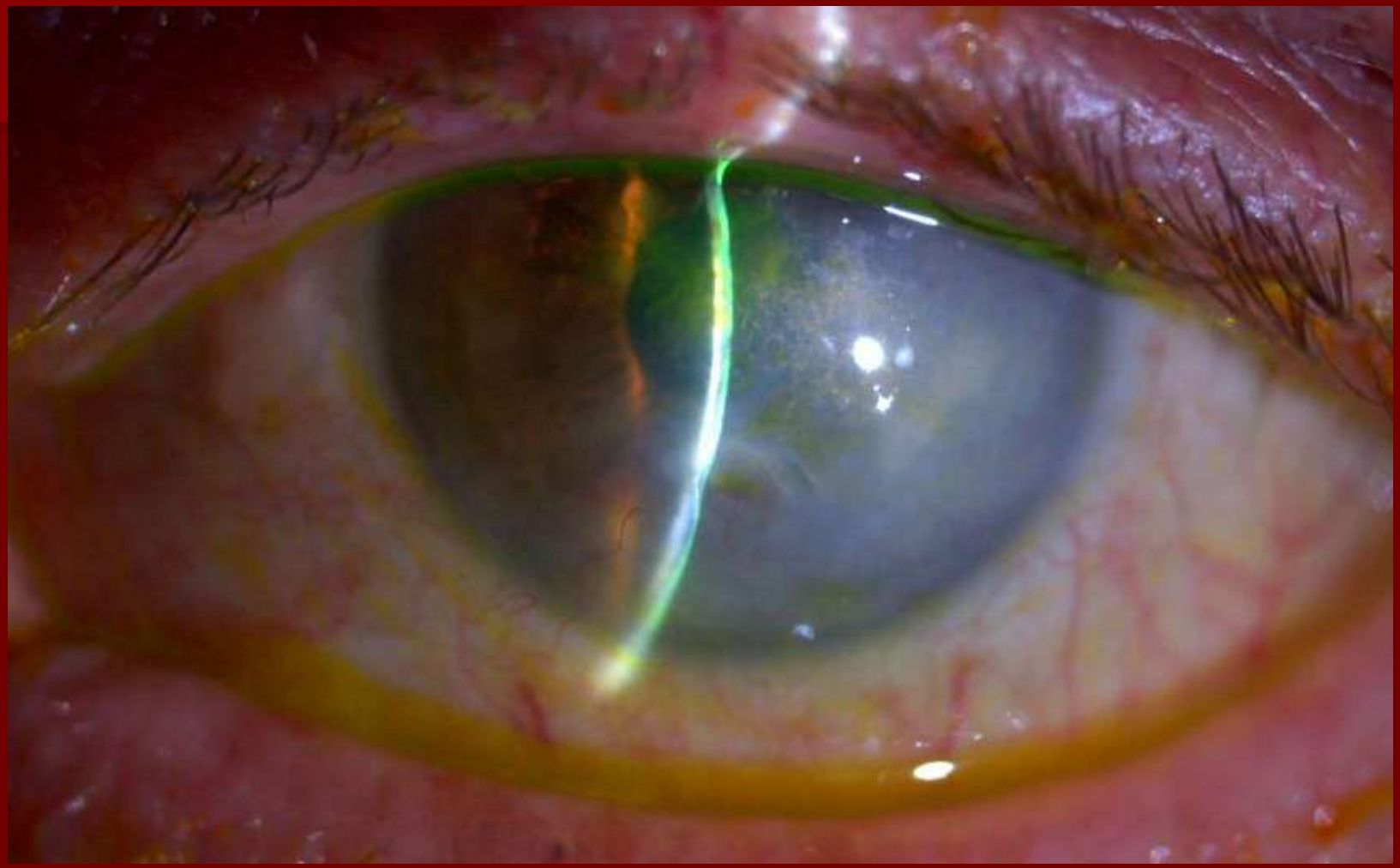
Slit Lamp Exam

Fluorescein stained cornea showing central epithelial defect with diffuse area of temporal interstitial haze. Corneal vascularization inferiorly.

Slit Lamp Exam

Central dendritic epithelial defect with pooling inferiorly.

Slit Lamp Exam



Stromal and epithelial irregularities

Assessment / Differential Dx

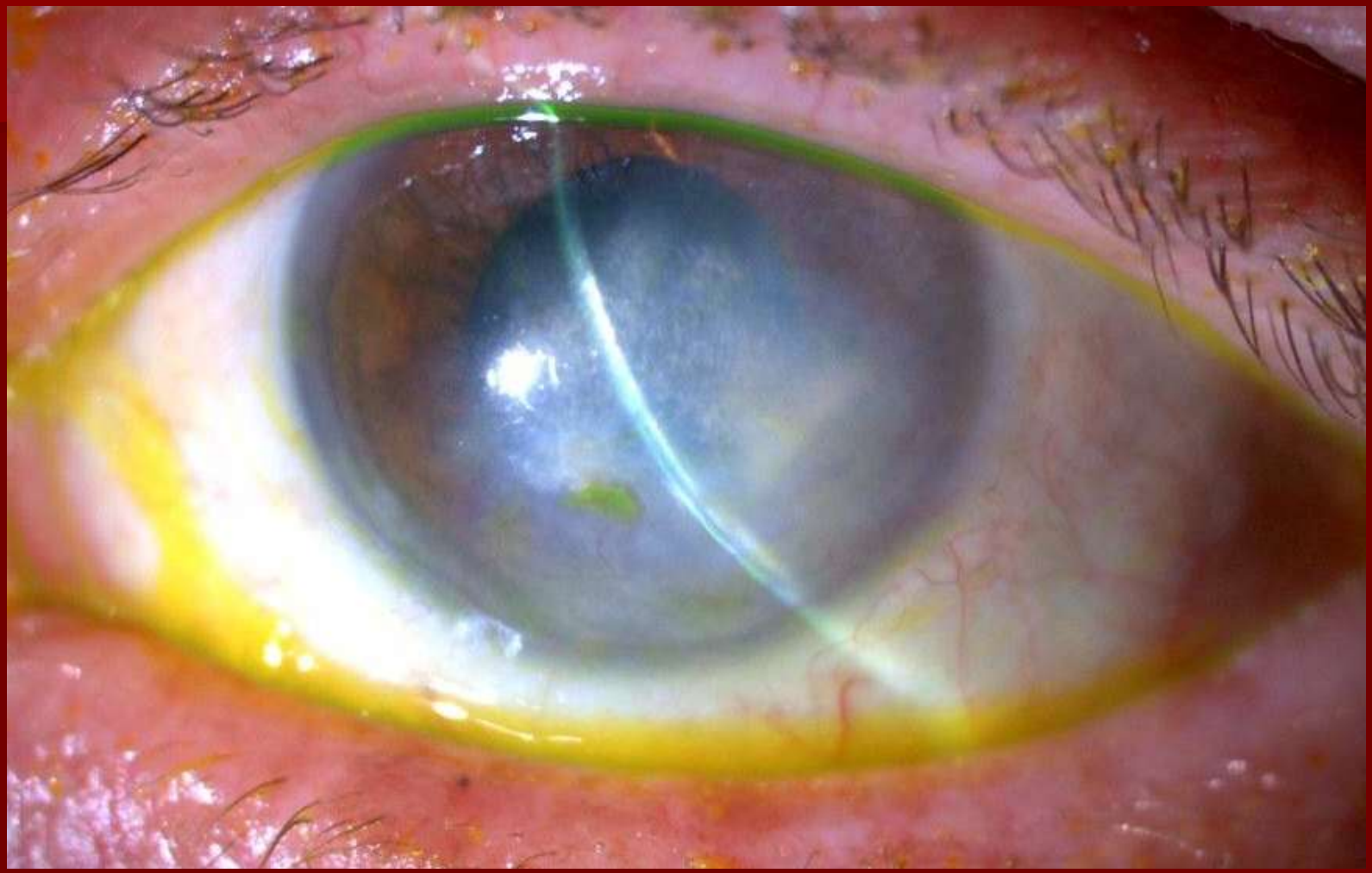
- 54yo white male with history of recurrent visual complaints who presents with exam findings of a dendritic epithelial keratitis along with interstitial keratitis most concerning for HSV infection.

- DDx
  - HSV epithelial and interstitial keratitis
  - Varicella zoster keratitis
  - Acanthamoeba keratitis
  - Syphilis
  - Mumps keratitis

Course

- Pt was treated for HSV keratitis with:
  - Acyclovir 400mg po qid
  - Trifluridine drops OS q4hr
- At 1 week follow-up, VA improved to 20/160

Slit Lamp Exam



Resolved dendritic lesion, corneal haze, stromal and epithelial irregularities

Slit Lamp Exam

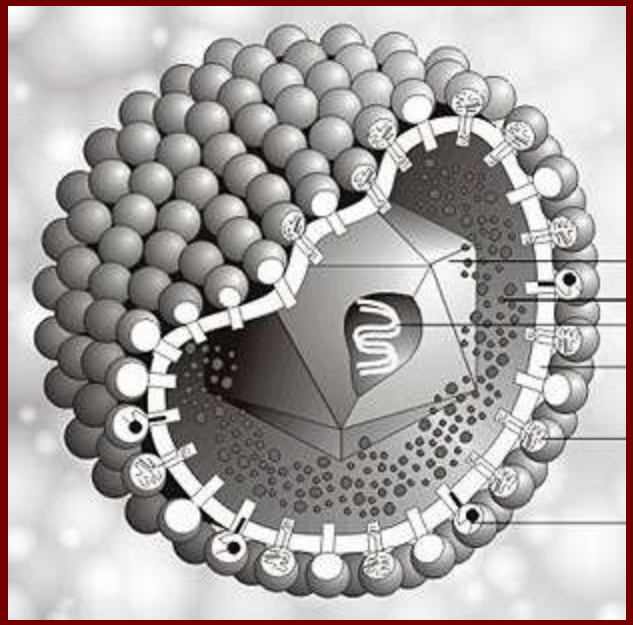
Larger magnification of stromal and epithelial irregularities

Course

- After this, pt missed several appointments, but returned 3mo later and had tapered self off all medications.
- VA at this time was 20/30, but prednisone drops and po acyclovir were restarted.
- Again pt did not return for following appointments, but came back 9 months later with recurrent symptoms after taking course of po steroids for COPD exacerbation.
- Once treatment was again initiated, pt did not keep subsequent appointments and returned 1.5yrs later with VA OS of HM.

Human Herpesviridae

- Core of linear dsDNA enclosed by icosahedral protein capsid, surrounding protein tegument, and an envelope studded with viral glycoproteins
- Class includes:
  - Herpes simplex virus 1 and 2 (HHV-1,2)
  - Varicella zoster virus (HHV-3)
  - Epstein-Barr virus (HHV-4)
  - Cytomegalovirus (HHV-5)
  - Herpes lymphotrophic virus (HHV-6)
  - Roseolovirus (HHV-7)
  - Kaposi's sarcoma associated virus (HHV-8)



(2)

- Viral progeny destroys infected cells
- All establish latency in host (ex. HSV may establish in trigeminal ganglion)

Herpes Simplex Virus

- Overview
  - ~100% of humans >60yo at autopsy have HSV in trigeminal ganglia
  - 1/3 population get recurrent infection
  - HSV-1 vs. HSV-2
  - Age of acquisition is increasing
  - Spread is through direct contact with infected lesion or secretion
  - Primary HSV-1 infection usually presents as upper respiratory tract infection
  - Most commonly becomes latent in trigeminal ganglion and reactivation may affect any branch
  - Causes a spectrum of disease

HSV – Primary Ocular Infection

- Usually occurs as unilateral blepharoconjunctivitis
- Pt may have follicles in conjunctiva and palpable pre-auricular lymph nodes
- Differentiating from adenovirus infection:
  - HSV shows cutaneous or eyelid margin vesicles
  - HSV may develop dendritic epithelial keratitis
  - Adenovirus may form conjunctival pseudomembranes
- Diagnosis
  - Viral culture
  - Antigen detection
  - DNA detection, real-time PCR[4]
- Management
  - Self limited
  - PO antivirals speed recovery

(3)

HSV – Recurrent Ocular Infection

- Pathway
  - Reactivation in sensory ganglion → transport down the axon to the nerve ending → manifest infection
- Associations
  - No confirmed association between environmental factors
  - Bilateral disease and multiple recurrences should raise concern for immune compromise (ex HIV)
- Forms of disease:
  - Blepharoconjunctivitis
  - Epithelial keratitis
  - Stromal Keratitis
  - Iridocyclitis (anterior uveitis)

HSV – Epithelial Keratitis

- Presentation
  - Foreign body sensation, photophobia, injection, blurred vision
  - Dendritic epithelial ulcer with terminal bulbs
  - Stromal edema
  - Resolution can leave "ghost dendrites"

(5)

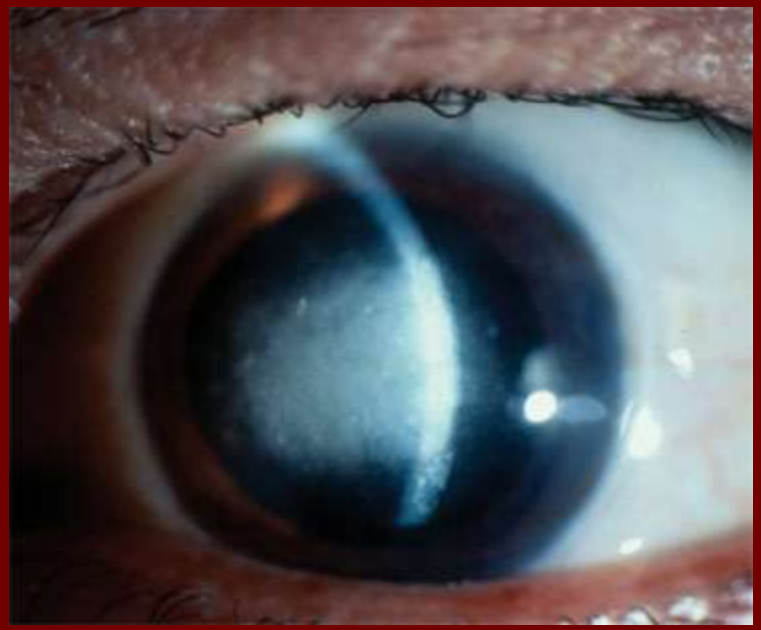
- Management
  - Resolves spontaneously in most cases
  - Antiviral therapy shortens course and reduces associated herpetic neuropathy
  - Wiping debridement
  - Topical trifluridine 1% 8x/day (stop within 10-14days)
  - Oral Acyclovir
  - Topical corticosteroids are contraindicated in active epithelial disease

HSV – Stromal Keratitis

- Most common cause of infectious corneal blindness in the United States.
- Recurrence increases visual morbidity
- Characterized by [6]
  - breakdown of the normal barrier to blood and lymph angiogenesis in the cornea
  - Increase in antigen presenting cells
  - Neutrophilic infiltrate
- May present as:
  - Herpetic interstitial keratitis
  - Herpetic disciform keratitis
  - Herpetic necrotizing keratitis

Herpetic Interstitial Keratitis

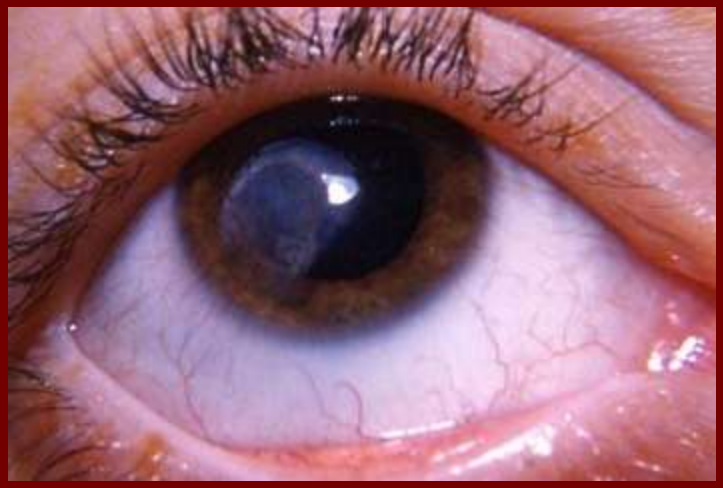
- Causes interstitial haze and whitening of the stroma without epithelial ulceration
- Difficult to distinguish old scar from active disease
- Recurrent episodes are associated with corneal vascularization



(7)

Herpetic Disciform Keratitis

- Presents as corneal stromal and epithelial edema, but is primarily due to inflammation of the endothelium and subsequent dysfunction
- Exam will show disc-shaped stromal edema and keratic precipitates
- May also be caused by VZV and is indistinguishable



(8)

Herpetic Necrotizing Keratitis

- Severe, rapid progression of suppurative corneal inflammation
- Will appear similar to bacterial or fungal keratitis

(9)

Management

- Eyelid involvement
  - Topical acyclovir ointment
  - Skin care/cool compresses
  - Trifluridine if lid margin involved
- Adult with primary herpetic disease
  - Acyclovir 400mg po 5x/day for 7-14days
- Conjunctivitis
  - Trifluridine drops 5x/day
- Corneal epithelial disease
  - Trifluridine 9x/day OR
  - Acyclovir 400 po 5x/day
  - Cycloplegic if anterior chamber reaction
  - Rapid tapering of topical steroids if used
  - Debridement

Management

- Herpetic Eye Disease Study (HEDS-I) [10]
  - Prospective, multicenter clinical trial that began in 1990s
  - Purpose and Results
    - Evaluate the efficacy of topical corticosteroids in treating HSV stromal keratitis in conjunction with topical trifluridine → patients who received topical corticosteroids had faster resolution of the stromal keratitis and fewer treatment failures.
    - Evaluate the efficacy of oral acyclovir in treating HSV stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine → No apparent benefit in the addition of oral acyclovir to the treatment regimen of topical corticosteroid and topical antiviral
    - Evaluate the efficacy of oral acyclovir in treating HSV iridocyclitis in conjunction with corticosteroids and trifluridine → numbers enrolled too small to achieve statistical significance, but the trend suggested adding oral acyclovir to pts with iridocyclitis was associated with lower number of treatment failures.

Management

- Herpetic Eye Disease Study (HEDS-II) [10]
  - Purpose and Results
    - Determine if early treatment with oral acyclovir of HSV ulcerations involving the corneal epithelium prevented progression to stromal keratitis and iridocyclitis → no benefit in preventing progression found
    - Determine the efficacy of low-dose oral acyclovir in preventing recurrent ocular HSV infection → 41% reduction in epithelial disease and 50% reduction in stromal disease
    - Determine the role of external factors (ex UV light, trauma, stress) on the induction of ocular HSV infections → no associations proved significant

Management

- Surgical
  - Reserved for visually significant stromal scarring
  - Must not have active disease
  - Will be on prophylactic oral antiviral therapy
  - Techniques:
    - Penetrating Keratoplasty
      - 80% chance of success if no signs of infection/inflammation for minimum of 6 months before surgery
    - Deep Anterior Lamellar Keratoplasty (11)
      - Study involving 52 eyes with stromal scars from HSV interstitial keratitis, intact endothelium, and no active disease
      - 52% had post-op BCVA of 20/20 and 80% of 20/30 or better
      - No rejection or recurrence in 31 month follow-up period
      - Antiviral prophylaxis still required
    - Amniotic Membrane Transplants

Thank you.

References

1. Basic and Clinical Science Course. DNA Viruses: Herpesvirus. American Academy of Ophthalmology. 8:105-117, 2010.
2. Image - http://mibiolaboratorio.blogia.com/temas/m-jose.-p.php
3. Image - http://www.dermapics.com/herpes/herpes-eye-b1.jpg
4. Hlinomazova Z et al. The treatment of HSV1 ocular infection using quantitative real-time PCR results. Acta Ophthalmology, Epub, 2010 Jun.
5. Image - http://www.avclinic.com/herpes_simplex.htm
6. Hazlett LD et al. Reviews for immune privilege in the year 2010: immune privilege and infection. Ocular Immunology and Inflammation. 18(4):237-43, 2010 Aug.
7. Image - http://odlarmed.com/wp-content/uploads/2009/05/cls_july_a09_fig06.jpg
8. Image - http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Disciform-keratitis-due-to-herpes-simplex-virus-active.html
9. Image - http://www.revophth.com/index.asp?page=1_430.htm
10. http://www.nei.nih.gov/neitrials/static/study37.asp
11. Sarnicola V et al. Deep anterior lamellar keratoplasty in herpes simplex corneal opacities. Cornea. 29(1):60-4, 2010 Jan.