ABSTRACT

Typically, ocular herpes simplex presents as a unilateral follicular conjunctivitis or keratitis before adulthood. In this case, a sixty year old female presents with primary herpes simplex which manifests as a bilateral erosive-ulcerative blepharoconjunctivitis.

OUTLINE

I. Case History
   a. Patient demographics
      i. 60 year old Native American Female
   b. Chief complaint
      i. Patient presents to the emergency room complaining of mild itch and irritation in both eyes for the past 3 days. Her vision has become blurry and her left eye has become increasingly irritated over the past four hours.
   c. Ocular and medical history
      i. Ocular: unremarkable
      ii. Medical: remarkable for post-traumatic stress disorder, atrial fibrillation, chronic obstructive pulmonary disease, asthma and atopic disease.
   d. Medications
      i. Fluoxetine, warfarin, albuterol inhaler, formoterol fumarate inhalation powder, montelukast sodium, mometasone furoate, simvastatin, diltiazem and ranitidine
   e. Other information
      i. Patient was taking oral prednisone 60 mg daily for 1 month after hypersensitivity reaction to tetanus/pertussis vaccination. Medication was discontinued 3 days prior to initial ocular symptoms. Patient also reports traumatic car accident one week prior.

II. Pertinent Findings – July 18, 2011: Four days after initial presentation
   a. Clinical
      i. Initially patient presents with swollen left upper and lower eyelids (Image 1), excessive mucopurulent discharge with associated conjunctival injection, chemosis and papillae reaction; mild punctate epithelial erosions superiorly on left cornea.
      ii. Patient develops bilateral red, ulcerative lesions on the medial and nasal aspect of the superior eyelid margin, erosion on the intermarginal portion of the left upper eyelid and associated severe edema of the upper and lower left eyelids.
b. **Physical**
   i. Patient denies fever, pain or neuralgia.
   ii. Negative preauricular adenopathy

c. **Laboratory studies**
   i. Serum testing

<table>
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<th>Test</th>
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<td>Creatinine</td>
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<tr>
<td>Estimated glomerular filtration rate</td>
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   ii. Negative for MRSA

III. **Differential Diagnosis**
   a. *Initial presentation – July 15, 2011*

   Moderately swollen left upper and lower eyelids (Image 1). Mucopurulent discharge OS with associated conjunctival injection, chemosis and moderate papillae reaction; mild punctate epithelial erosions superiorly on left cornea

   i. Primary Diagnosis – Bacterial conjunctivitis: characterized by mucopurulent discharge, papillae and chemosis, typically the cornea is not involved.

   Amount and type of patient’s discharge are consistent with this presentation

   ii. Alternative Diagnoses

      1. Gonococcal conjunctivitis
         - Hyperacute red eye with severe mucopurulent discharge
         - Possible pseudomembrane or true membrane

      2. Epidemic keratoconjunctivitis
         - Acute follicular conjunctivitis with excessive watery discharge, hyperemia and chemosis
         - Pseudomembranes or true membranes can occur

      3. Herpetic keratitis
         - Pain, hyperemia, blurred vision
         - Small, clear raised vesicles or characteristic dendritic corneal lesion

   IMAGE 1. Initial presentation: note edema of left eyelids. Excessive discharge has been removed.
b. Day Two – July 16, 2011

Mucopurulent discharge resolved. New moderate watery discharge; new area of circular erosion on the intermarginal portion of the left upper eyelid with associated lid edema (Image 2). 4mmx3mm superficial epithelial corneal defect superiorly and scattered punctuate epithelial erosions inferiorly.

i. Primary Diagnosis – Herpes zoster virus: Painful skin vesicles along a dermatome that respect the midline

New lesion on left upper eyelid is consistent with the vesicular rash characteristic of herpes zoster. The lesion is present within the area of innervation of the first branch of the trigeminal nerve.

ii. Alternative

1. Herpes simplex virus
   - Skin vesicles, typically along the eyelid margin; can be associated with a unilateral conjunctivitis.

2. Impetigo
   - Pimple-like sore surrounded by erythematic area caused by bacteria infecting open skin

c. Day Four – July 18, 2011

Four days after initial presentation, patient develops new red, ulcerative lesions on nasal aspect of the right superior eyelid margin with mild lid edema (Image 3). Severe edema and lesions on the left lids are stable (Image 4).
Visual acuity is stable at 20/25 in the right eye and decreased in the left eye to 20/200. Pupils and extraocular motilities are normal in both eyes.

Biomicroscopy of the right eye reveals minimal discharge and normal cornea, iris, lens and anterior chamber.

Exam of the left eye reveals severe chemosis with moderate injection along with a follicular reaction. The corneal epithelial defect is increased to 8mm x 6mm and located centrally and three small subepithelial punctuate erosions are present nasally at the limbus. The iris, lens and anterior chamber are clear.

Corneal sensitivity is poor in each eye.

Dilated exam reveals clear vitreous and intact retina.

Patient reports episode of chicken pox at age 10, denies previous cold sore or herpes infection. Denies any additional lesions elsewhere on her body similar to lid lesions.

i. Primary Diagnosis – Herpes simplex virus

Herpes simplex usually presents unilaterally but can present bilaterally. It is more common in patients with atopic disease and of a younger age. The lid lesions are characteristic of herpes simplex blepharitis.

ii. Alternative Diagnosis – Herpes zoster virus

Herpes zoster virus is not likely at this stage of presentation given the bilaterality of rash and lid involvement. Typically a zoster rash is preceded by a symptomatic prodome of moderate pain and neuralgia along the involved dermatome. This patient denies any pain, tingling or numbness.

d. Final diagnosis – Herpes simplex blepharoconjunctivitis

The patient’s lesions are most consistent with erosive-ulcerative herpes simplex lesions. The areas of involvement appear thin and ulcerated, especially along the lid margin, and are located mainly at the lid margin. The cornea defect was most likely due to mechanical stress from the amount of discharge and lid edema.

IV. Diagnosis and Discussion

a. Herpes simplex virus (HSV)

i. HSV is ubiquitous, highly contagious and able to remain dormant within human nerve ganglia

ii. Ninety per cent of people over sixty years of age are positive for HSV-1, the strain that most commonly causes ocular infections

iii. HSV-1 can remain dormant in nerve ganglia and reactivate along the ganglion if triggered

1. Common triggers include stress, UV radiation, fever, immunocompromise and trauma.

b. Herpes simplex ocular implications: Classic presentation

i. Primary
1. Signs
   - Unilateral
   - Follicular blepharoconjunctivitis
     i. Erosive-ulcerative – Single or several erosions 1-3mm at the intermarginal portion of the eyelid and/or 1-3 ulcers 3-5mm adjacent to the lid margin; more common than vesicular
     ii. Vesicular – Crop of vesicles, usually pinhead in size with associated erythematous base unilaterally
       - Periocular dermatitis
       - Superficial keratitis
       - Lid involvement is much more common than corneal (93% vs 60%)

2. Symptoms
   - Redness, discharge, itch or irritation, lid edema

3. Average age: 25 years old

4. Initial infection usually has a more dramatic presentation than a recurrent episode, healed within 2-3 weeks

ii. Secondary
   1. Signs
      - Unilateral
      - Dendritic keratitis
      - Stromal keratitis
      - Uveitis

2. Symptoms
   - Redness, pain, photophobia, tearing

3. Typically appears in adults

4. Signs are more likely inflammatory vs. infectious due to an antibody immune response

c. Atopic Disease
   Eczema, asthma, allergic rhinitis
   i. Hypersensitivity type I reaction causing chronic inflammation
      1. Greater sensitivity to external allergens
      2. Increased IgE levels
   ii. Defective epidermis, innate immune system dysregulation
      1. Increased risk of infection due to poor skin barrier
      2. Allows for increased viral replication vs non-atopic people once infected
   iii. Association with herpes simplex
      1. Five times greater risk of infection vs. normal population
      2. Higher risk of bilateral infection: 12% in atopic disease patients vs. 2% in normal population
      3. Increased sensitivity to allergens leads to an exaggerated response
4. Defective innate immune system leads to increased susceptibility to herpes simplex virus
5. More commonly associated with epithelial vs. stromal reactions and infectious vs inflammatory etiology
d. Primary infection at 60 years of age
   i. 90% of population at 60 years old has had initial simplex infection
   ii. Higher incidence with bilaterality vs. recurrent disease
   iii. Only 5% of herpes simplex infections are primary
   iv. Questionable source of inoculation
       1. Patient does have grandchildren ages 3-5 living with her
e. Bilateral
   i. 3-12% of population have bilateral infection
       1. Of the 12%, 28% were found to have atopic disease
       ii. At the initial infection, 7.3% of patients have bilateral involvement
       iii. Simplex is usually unilateral due to antibodies formed to the virus after the initial infection
f. Given the patient’s state of immunocomprise from oral prednisone and her level of atopic disease, there is substantial evidence as to why a 60 year old could become infected by simplex. The primary infection of simplex is usually an exaggerated response which was only exacerbated by her atopic disease, leading to a severe reaction and delayed recovery.

V. Treatment and management
   a. Treatment and response
      i. Valacyclovir 1 g TID PO x 3 days, 1 g BID PO x 14 days, 500 mg qDaily x 6 months
         1. Acyclovir prodrug
            - Valacyclovir has five times the bioavailability
              1000mg TID valacyclovir has the same effect as 400mg 5 times a day acyclovir
            2. Decreased dose to allow for prolonged treatment, especially while on topical steroids
            3. Treatment for 6 months for prophylaxis
               - 400 mg Acyclovir BID PO reduced risk of recurrence drastically and risk of more severe disease like stromal keratitis
            4. Herpetic Eye Disease Study
               - HEDS II
               - Oral acyclovir to prevent recurrent simplex infections
      ii. Moxifloxacin 0.5% sol. 1 gtt QID OS x 1 month
         1. Prevent secondary bacterial infection, especially given corneal compromise
         2. Continued until corneal epithelium healed
      iii. Fluorometholone 0.1% sol. 1 gtt QID x 2 weeks, TID x 2 weeks, BID x 2 weeks, then qDaily x 3 months
1. Indicated for pseudomembranous conjunctivitis and to reduce scarring risk after epithelial closing
   iv. Ciprofloxacin 0.3% ointment nightly OS and QID on lid lesions
   1. Antibacterial coverage for lid lesions and cornea along with lubrication for epithelial defect  
   v. Carboxymethylcellulose 1 gtt QID OU
   1. Lubrication to prevent further mechanical erosion of cornea
   vi. Avoided trifluridine due to risk of corneal toxicity on already disrupted cornea. As corneal defect was most likely mechanical, no need for topical antiviral; any viral shedding onto the cornea would be treated by the oral valacyclovir.

b. Response to treatment
   i. Oral valacyclovir was initially started at the first sign of a vesicular rash for treatment of a possible herpes infection. The lid edema, erosions and ulcerations progressed for 2 days while on oral treatment. The epithelial erosion, which was most likely mechanical, worsened over the first 2 days and resolved after 2 weeks of treatment.
   ii. Typically a primary herpes ocular infection would be resolved at 3 weeks with treatment. This patient showed delayed healing and experienced prolonged symptoms. This may be related to her atopic disease and poor immune function. The lid edema and amount of discharge was so severe that a decrease immune reaction would only allow for a longer duration of infection.
   iii. Timeline after treatment was initiated
      1. Blepharitis
         - Erosions/ulcers: improved in 2 weeks, resolved in 1 month
         - Edema: improved in 1 month, resolved in 6 weeks
      2. Conjunctivitis
         - Pseudomembrane resolved in 1 week
         - Discharge improved slowly and resolved at 5 weeks
      3. Corneal defect
         - Slowly improved with full resolution at 3 weeks

VI. Conclusion
   a. Herpes simplex can have a bilateral presentation and in those cases is easily distinguishable from herpes zoster.
   b. While clinical presentation is usually sufficient for diagnosis of herpes simplex, in unusual presentations, laboratory and microbiology testing may be beneficial.
   c. With any suspicion of herpes, initial follow up should be within 1-2 days. Herpes can progress rapidly and earlier detection and treatment may help limit the progression and long term residual sequelae.
   d. Given improved hygiene, primary herpes simplex infections may be occurring later in life than previously thought. Initial infections were most
common during childhood up until 3-5 years ago. Now, the primary infections are most commonly during adolescence and early adulthood.
e. Patients with atopic disease presenting with blepharitis, conjunctivitis and/or keratitis should be carefully monitored for possible herpes simplex given high risk due to compromised immunity.

VII. Bibliography