CORNEAL ULCERS: INFECTIOUS OR STERILE?
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FINANCIAL DISCLOSURES

• I have received honorarium from: Essilor / OOGP
• Clinical Assistant Professor – University of Houston, College of Optometry
• Opinions from this lecture are my own

COURSE EXPECTATIONS

• Introduction
• Etiologies
• Pathophysiology
• Clinical features
• Cases
• Diagnostic assessment
• Treatment and management

INFECTIOUS VS. STERILE ULCERS
UNDERSTANDING THE DIFFERENCES IN ETIOLOGY & PATHOPHYSIOLOGY

SIGNIFICANCE IN...

• Differentiation:
  • Treatment & management
• Management:
  • Both may result in visually significant opacification
  • Both may result in ocular morbidity

CORNEAL ULCERS

• Clinical Presentation:
  • Infectious & sterile ulcers both require a significant defect of the overlying epithelium
  • Stains with fluorescein and lissamine green/rose bengal
  • Presence of inflammation
  • Non-ulcer breaks of the overlying epithelium
  • Erosions
  • Trauma
**INFECTIOUS ULCERS**

- Results from active infection of the cornea (microbial keratitis):
  - Direct pathogen invasion
  - Microbes include bacteria, viruses, parasites, and fungus
- Risk factors: varies for underlying etiology
  - Contact lens wear and/or abuse
  - Trauma
  - Age
  - Geography

**PATHOPHYSIOLOGY OF INFECTIOUS ULCERS**

- Invasion of pathogen
- Immune response:
  - Polymorphonuclear neutrophils (PMNs) to site → Release of matrix metalloproteases (MMPs) → Ulcer
- Healing vs. Non-Healing:
  - Healing: Macrophages clear debris → Scarring → potentially vision loss
  - Non-healing: Progressive keratolysis → perforation

**CLINICAL FEATURES OF INFECTIOUS ULCER**

- Pain and photophobia
- Lid edema
- Hyperemia
- Large with irregular borders
- Corneal reaction
- Anterior chamber reaction

**STERILE ULCERS**

- Results as a complication of inflammation
- Etiologies of inflammation:
  - Ocular surface instability
  - Autoimmune diseases
  - Ocular surgeries
  - Others

**STERILE ULCERS: ETIOLOGIES**

- Ocular surface instability:
  - Neurotrophic keratopathy
  - Exposure keratitis
- Autoimmune conditions:
  - Rheumatoid arthritis
  - Sjogren's Syndrome
  - Wegner’s Granulomatosis
- Contact lenses
- Vitamin A deficiency
- Ocular surgeries
- Mooren’s Ulcer

**PATHOPHYSIOLOGY OF STERILE ULCER**

- Compromised tear film / unstable ocular surface
- Immune response: PMNs to site → Release of MMPs → Ulcer
- Healing vs. Non-Healing:
  - Healing: Macrophages clear debris → Scarring → potentially vision loss
  - Non-healing: Progressive keratolysis → perforation
CLINICAL FEATURES OF STERILE ULCER

- Persistent epithelial defects
- Unstable tear film
- Aqueous deficiency
- Minimal pain
- Anterior corneal edema
- Corneal hypoesthesia
- Smooth, regular borders

<table>
<thead>
<tr>
<th>Infectious Ulcer</th>
<th>Factors</th>
<th>Sterile Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger</td>
<td>SIZE</td>
<td>Smaller</td>
</tr>
<tr>
<td>Central</td>
<td>LOCATION</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Decreased</td>
<td>VISION</td>
<td>No change</td>
</tr>
<tr>
<td>Irregular, indistinct</td>
<td>BORDERS</td>
<td>Round, distinct</td>
</tr>
<tr>
<td>Extensive</td>
<td>ADJACENT CORNEAL REACTION</td>
<td>Limited</td>
</tr>
<tr>
<td>Moderate-Severe</td>
<td>CHAMBER RXN</td>
<td>None-Mild</td>
</tr>
<tr>
<td>&gt; 2 mm in size</td>
<td>INFILTRATES</td>
<td>0.75 to 1.0 mm in size</td>
</tr>
<tr>
<td>Moderate-Severe</td>
<td>PAIN</td>
<td>Mild</td>
</tr>
<tr>
<td>Purulent</td>
<td>DISCHARGE</td>
<td>Mucopurulent</td>
</tr>
</tbody>
</table>

CASE: 65 YRO AAF

- CC: Outside referral for corneal ulcer OD
- HPI:
  - Dx by ER 2 weeks prior
  - Rxed unknown ointment q6h, moxifloxacin gtt every hour
  - Associated symptoms:
    - Achiness
    - Serous discharge that is minimal at this visit
    - No pain

CASE

- POH: Advance cataract OD
- PMH: arthritis, HTN
- Medications: Ibuprofen, Lisinopril, cetirizine
- Allergies: NKDA, seasonal allergies

CASE

- VA (ex): OD LP, OS 20/25 PH 20/20
- Pupils: equal, round, reactive, [-] AFD
- BOM: USA OD, OS
- IOPs: OD: soft; no reading on NCT
  - OS: 17 mmHg
- CF: PFTC OD, OS
**SOD**

<table>
<thead>
<tr>
<th>ADNEXA</th>
<th>WNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIDS/LASHES</td>
<td>Thickened eyelids, cloudy / minimal MG expression, telangectasia</td>
</tr>
<tr>
<td>CONJ</td>
<td>Perilimbal injection 360 with 1 + inferior injection</td>
</tr>
<tr>
<td>CORNEA</td>
<td>Arcus, 2mmHx3mmV epithelial defect (+) NaFl with smooth borders overlying infiltrative haze</td>
</tr>
<tr>
<td>AC</td>
<td>(-) C/F</td>
</tr>
<tr>
<td>IRIS</td>
<td>Flat, brown</td>
</tr>
<tr>
<td>LENS</td>
<td>Advanced cortical opacification</td>
</tr>
</tbody>
</table>

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**Factor Considerations**

**Size**
- Infectious ulcers tend to be larger than 2 mm
- Sterile ulcers tend to be smaller than 2 mm

**Location**
- Paracentral defects could go either way but the closer to visual axis, more likely to be infectious.
- Other factors will help determine this (adjacent corneal reaction, borders)

**Vision**
- Visual axis obscuration
- Adjacent corneal reaction causing decreased vision

**Is this corneal ulcer infectious or sterile?**

**Factor**
- Shape of lesion: round/oval vs. irregular
- Edges: smooth borders vs. heaped edges

**Adjacent Corneal Reaction**
- Paracentral defects could go either way but the closer to visual axis, more likely to be infectious.
- Other factors will help determine this (adjacent corneal reaction, borders)

**Anterior Chamber Reaction**
- Stronger AC reaction indicates more infectious
- Hypopyon more likely to be infectious but can occur in non-infectious
IS THIS CORNEAL ULCER INFECTIOUS OR STERILE?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrates</td>
<td>• Diffuse infiltration tends to be more infectious</td>
</tr>
<tr>
<td></td>
<td>• Small, round infiltrates are more likely to be sterile</td>
</tr>
<tr>
<td>Pain</td>
<td>• Sterile ulcers may present with mild ulcers or none at all</td>
</tr>
<tr>
<td></td>
<td>• Infectious presents with significant pain and photophobia</td>
</tr>
<tr>
<td>Discharge</td>
<td>• Majority has reflex (serous) discharge</td>
</tr>
</tbody>
</table>

Factors | Case
--------|------
SIZE     | Larger
LOCATION| Paracentral
VISION   | No change
BORDERS  | Somewhat irregular with smooth edges
ADJACENT CORNEAL RXN | Inactive > active
CHAMBER RXN | None
INFLTRATES | Distinct haze, minimal edema
PAIN     | None
DISCHARGE| Serous

CASE: CONSIDERATIONS

• Decreased vision:
  • Lens opacification causing UPI
  • Exudate
  • Prior inflammation?
  • Defect with rolled/smooth edges
  • Lack symptoms
  • Corneal sensitivity testing: decreased sensitivity

CASE

• Assessment:
  • Neurotrophic keratopathy OD
  • Advance cataract OD – contributing to majority of decreased VA

• Plan:
  • DC Moxifloxacin. Start Tobradex QID OD with f/u in 2 days. Refer to PCP for IgG/IgM testing for HSV & VZV.
  • Upon keratitis resolution, refer for cataract extraction OD.

FOLLOW-UP 2 WEEKS LATER TOBRADEX + BCL

CASE
CASE: 47 YRO HM

• **CC:** Red, painful right eye
• **HPI:**
  - Onset 2 months ago
  - Associated symptoms: photophobia, redness
  - (-) trauma or CL wear
  - Saw OD who Rxed: Durezol 4/3/2/1 schedule and neomycin/polymixin-b/dexamethasone PRN.
  - Feels that condition has worsened

**POH:**

• “Eye infection” OD - 25-30 years ago treated with unknown drops
• **PMH:** (+) DM – Dx 1 month ago
• **MEDS:** Metformin, Durezol, Neomycin/Polymixin-B/dexamethasone
• **ALL:** NKDA

**VA:**

- OD 20/70, PH 20/60
- OS 20/200, PH 20/100

**EOMs:** USA OD, OS

**CF:** FTFC OD, OS

**Pupils:** Equal, round, reactive without AFD OD, OS

**Goldmann IOPs:**

- OD 11 mmHg
- OS 18 mmHg

**Factors**

<table>
<thead>
<tr>
<th>Case</th>
<th>Size</th>
<th>Location</th>
<th>Vision</th>
<th>Borders</th>
<th>Adjacent Corneal Rxn</th>
<th>Chamber Rxn</th>
<th>Infiltrates</th>
<th>Pain</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD OS</td>
<td>Larger</td>
<td>Pericentral</td>
<td>Decreased</td>
<td>Irregular, necrotic edges</td>
<td>Significant</td>
<td>UTT</td>
<td>Significant</td>
<td>Present</td>
<td>Serous discharge</td>
</tr>
</tbody>
</table>
CASE: CONSIDERATIONS

- New inflammation related to old inflammation?
- HSV / VZV
- Corneal sensitivity testing: Equal OD, OS

CASE: ASSESSMENT

- Infectious keratitis OS:
  - Resistance to antibiotic / worsening with steroids
- Etiologies to consider:
  - Pseudomonas – timeline not consistent with Pseudomonas
  - Fungus
  - Acanthamoeba

CASE: PLAN & REFERRAL

- Refer to corneal specialist for evaluation:
  - Active infection due to HSV / Fungus / Bacteria.
  - Besivance q1h.
  - Referral to county hospital.
- County hospitals: Positive culture for FUNGUS!

DIAGNOSTIC ASSESSMENT: ESSENTIAL EXAM

- History
- Risk Factors
- Clinical appearance
  - Remember the dilated fundus examination!

DIAGNOSTIC ASSESSMENT: OTHER TESTING

- Corneal sensitivity testing
- Anterior segment OCT
- External Photography

DIAGNOSTIC ASSESSMENT: ANCILLARY

- Corneal cultures:
  - Microscopy – stains
  - Lab cultures
  - Confocal microscopy
WHEN TO CULTURE: 3-2-1 RULE

• Size: 3 mm in size or wider
• Quantity: 2 or more ulcers
• Location: Within 1 mm of the visual axis

WHEN TO CULTURE

• Poor response to therapy
• Worsening
• Atypical bug
• High risk: Post-surgical, monocular, immunocompromised

STAIN VS. PLATES?

• Benefits of stain: prompt, in-office
• Benefits of culture: more variety in media
• Both types of culture increase likelihood of growth!

DIAGNOSTIC ASSESSMENT: COLLECTION

• Stains and cultures both require collection
• Anesthetic
• Areas to culture:
  • Cornea, conjunctiva, lid margin
  • Contact lenses, cases
• Collect at base and at edge
• Avoid purulent discharge
• Remove necrotic tissue

Stain Organism Considerations

<table>
<thead>
<tr>
<th>Stain</th>
<th>Organism</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram</td>
<td>Bacteria, fungi, microsporidia</td>
<td>Best for bacteria; can show up for fungus but not definitive</td>
</tr>
<tr>
<td>Giemsa</td>
<td>Fungi, Acanthamoeba, Microsporidia</td>
<td></td>
</tr>
<tr>
<td>Potassium hydroxide</td>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td>with calciofluor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid-fast stain</td>
<td>Mycobacterium, Nocardia</td>
<td></td>
</tr>
<tr>
<td>Periodic acid-Schiff</td>
<td>Fungi, Acanthamoeba</td>
<td></td>
</tr>
<tr>
<td>(PAS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Media Organism Considerations

<table>
<thead>
<tr>
<th>Media</th>
<th>Organism</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood agar</td>
<td>Bacteria, fungi</td>
<td>Does NOT detect Neisseria, Haemophilus, Moraxellia</td>
</tr>
<tr>
<td>Chocolate agar</td>
<td>Haemophilus, moraxela, neisseria</td>
<td></td>
</tr>
<tr>
<td>Sabouraud dextrose agar</td>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td>MacConkey</td>
<td>Gram negative bacteria</td>
<td>Useful for Pseudomonas due to lactose differentiation</td>
</tr>
<tr>
<td>Periodic acid-Schiff</td>
<td>Fungi, Acanthamoeba</td>
<td></td>
</tr>
<tr>
<td>Thioglycolate broth</td>
<td>Anaerobic, aerobic bacteria, fung</td>
<td></td>
</tr>
<tr>
<td>Lowenstein-Jensen medium</td>
<td>Mycobacterium, Nocardia</td>
<td></td>
</tr>
<tr>
<td>Non-nutrient agar with E.coli</td>
<td>Acanthamoeba</td>
<td></td>
</tr>
</tbody>
</table>
**CULTURE REPORTS:**

- Positive growth in 50-60% of collections
- Growth results:
  - Typical microbes: 2-14 days
  - Atypical microbes: Several weeks for growth
- Sensitivity report:
  - Effectiveness of anti-microbial agent
  - 1-2 days; 7 days; 14 days.

**CONFOCAL MICROSCOPY**

**EMPIRICAL TREATMENT: STERILE ULCERS**

- Address etiology \(\Rightarrow\) Decrease inflammation
- Topical treatment:
  - Topical steroids
  - Topical immunomodulators
- AMT, autologous serum, scleral contact lenses

**EMPIRICAL TREATMENT: INFECTIOUS ULCERS**

- Assumption is bacterial etiology
- Disadvantage \(\Rightarrow\) Messes up culture!
- Aggressive antimicrobial treatment:
  - Loading dose
  - Therapy q1-2h during night
  - Consider more than 1 anti-infective agent with alternation
  - Fortified antibiotics

**INFECTIOUS ULCERS: BROAD SPECTRUM**

- Fluoroquinolones (4th generation)
- Cephalosporins
- Aminoglycosides
- Tetracyclines
- Trimethoprim-sulfamethazole
- Fortified antibiotics

**INFECTIOUS ULCER: STEROIDS?**

- Steroids \(\Rightarrow\) Depressed immune system \(\Rightarrow\) Proliferation of microbe
- Avoid in first 24-48 hours if you suspect infectious!
- Inflammation Follows infection:
  - Steroid for Corneal Ulcer Trial (SCUT)
  - Large, randomized study: Role of steroids in corneal ulcer treatment
STEROID FOR CORNEAL ULCER TRIAL (SCUT)

- No differences at 3 months for measures of VA, scars, or rate of perforation
- Differences in subgroups: Those treated with steroids had better VA if...
  - Significant decreased vision
  - Central location
  - Deep ulceration
  - As long as it is not Nocardia

EMPIRICAL TREATMENT: UNSURE?

- Treat as infective for first 24-48 hours or epithelial closure
- If improvement \(\rightarrow\) likely infectious etiology
- If no improvement \(\rightarrow\)
  - 1) Inadequate therapy
  - 2) Wrong bug
  - 3) Not infectious

NON-MEDICAL MANAGEMENT

- Corneal collagen cross-linking
- Amniotic membrane transplantation
- Conjunctival flaps
- Corneal transplantation

SUMMARY

- Corneal ulcers are difficult!
- History, symptoms, and clinical features
- Consider cultures:
  - 3-2-1 Rule!
  - Worsening, poor immune system, monocular

QUESTIONS?
ZSKRUOCH@CENTRAL.UH.EDU

SUMMARY

- Treatment:
  - If unsure, assume active infection! Treat aggressive with antimicrobial agents for first 24-48 hours
  - Don't be afraid of steroids!
10. The Steroids for Corneal Ulcers Trial (SCUT): Secondary 12-Month Clinical Outcomes of a Randomized Controlled Trial. Muthiah Srinivasan...