Grand Rounds

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Patient

- HPI: 60 yo male with h/o pain, redness, photophobia, foreign body sensation and blurry vision in his left eye x 4 days. He states that he had similar problems in the past about 6 years ago

Patient History

PMH: CHF 2/2 dilated cardiomyopathy with pacemaker, EtOH abuse

POH: similar symptoms 6 years ago

Gtts: none

Meds: Spironolactone, Lasix, ASA, Carvedilol, Enalapril (poor compliance)

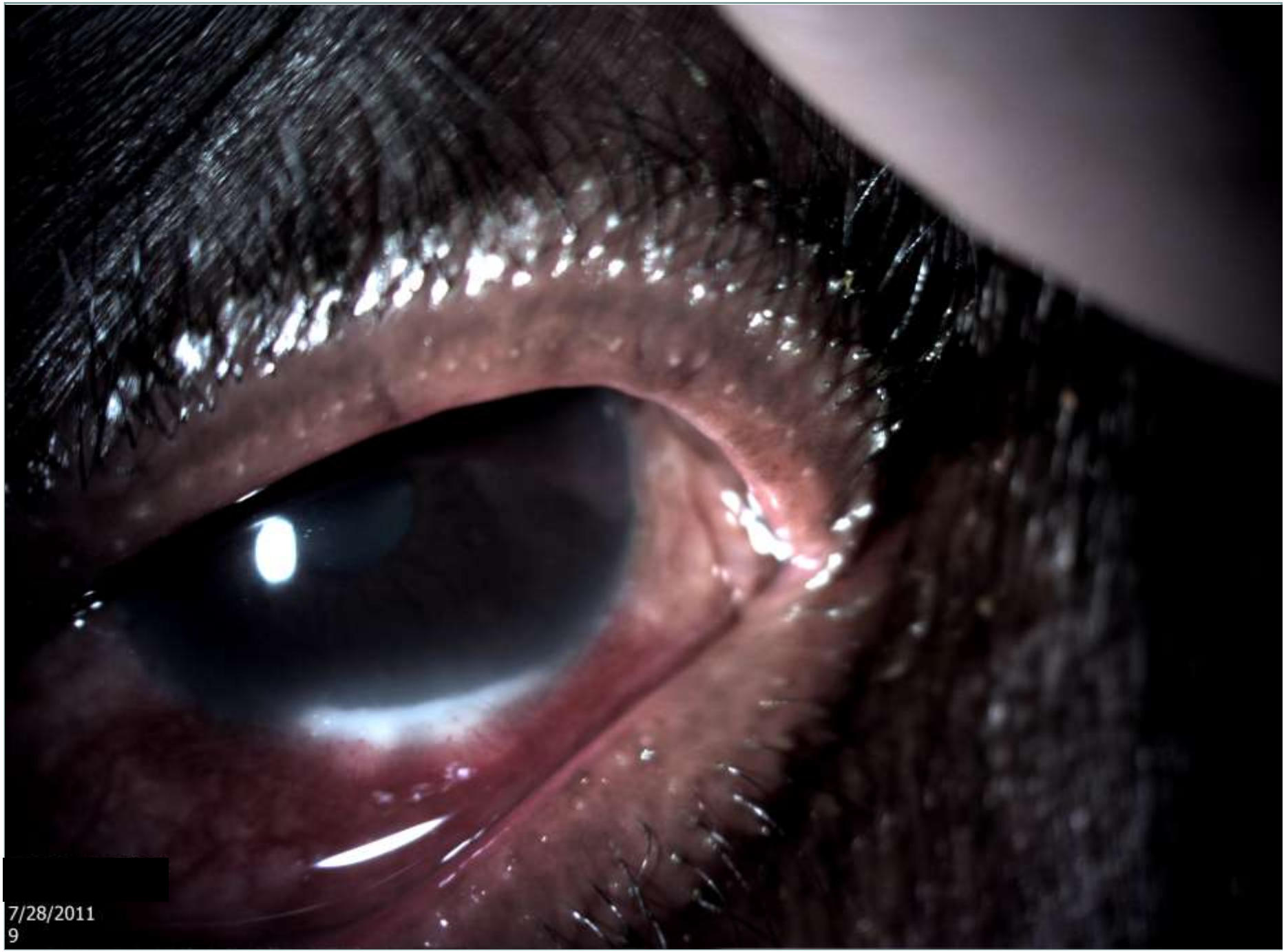
Allergies: nkda

FH: no glaucoma/blindness

SH: heavy alcohol use stopped 3 years prior, 10 pack years, no drug use

Exam

- dVA sc:
  - OD: 20/25 ph ni
  - OS: 20/40 ph 20/30
- Pupils: 4→2 ou. No apd
- EOM: full ou
- cVF: full ou
- Tapp: 15/6 @ 6:40am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SLE

- LLA: mgd ou. Trace Edema of LUL and LLL
- C/S: wnl od, 3+ inj os with chemosis
- K: PEEs ou. Inferior area of opacification at limbus
- A/C: wnl od, rare cell os, no hypopyon
- P/I r and r ou
- L: ns ou

DFE

- V: clear ou
- C/D: 0.3 ou, s and p ou
- M: flat ou, +flr ou
- V/P: wnl ou. No holes, tears, rd, heme ou

Differential Diagnosis

Ocular

- Infectious
  - Microbial – Staphylococcus (marginal), Streptococcus, Gonococcus, Moraxella, Haemophilus
  - Viral – HSV, HZV
  - Parasitic – Acanthamoeba
  - Fungal
- Mooren Ulcer
- Terrien marginal degeneration
- Furrow degeneration
- Exposure Keratopathy
- Dellen
- Rosacea
- Phlyectenulosis
- Fuch's Superficial Marginal Keratitis
- Traumatic/Post-surgical
- Trichiasis
- Poor Contact Lens fitting

Systemic

- Infectious
  - Microbial – TB, syphilis, Gonorrhea, Borreliosis, Bacillary dysentery
  - Viral – HZV, HIV, Hepatitis C
  - Helminthiasis
- Connective Tissue Disease
  - RA
  - SLE
  - Wegener's Granulomatosis
  - Polyarteritis Nodosa
  - Relapsing Polychondritis
  - Progressive Sclerosis and Scleroderma
  - Sjogren's syndrome
  - Behcet's syndrome
- Sarcoidosis
- Inflammatory Bowel Disease
- Alpha-1 antitrypsin deficiency
- Malignancy

History

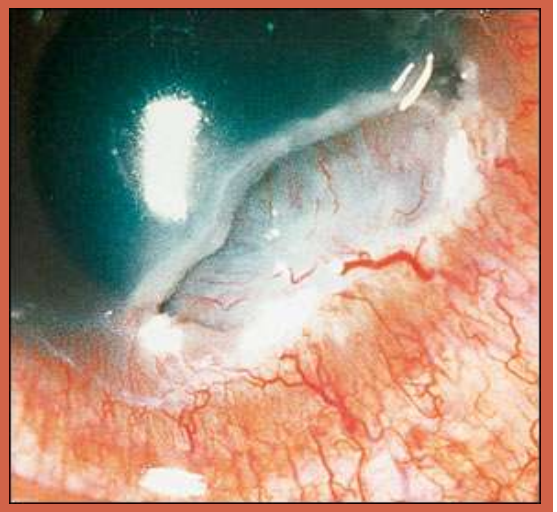
- A thorough history must be obtained including:
  1. Previous ocular history of infections including ocular and non-ocular herpetic disease
  2. Contact lens wear
  3. Current and previous medication
  4. Trauma
  5. Surgery
  6. Comprehensive review of systems should be obtained

Workup?

Workup?

- First rule out infectious process
- Labs
  - CBC
  - ANA
  - ESR
  - ANCA
  - FTA
  - RF

Peripheral Ulcerative Keratitis



- Term used to describe a group of destructive inflammatory diseases involving the peripheral cornea whose final common pathway is characterized by sloughing of corneal epithelium and keratolysis.
  - Crescent-shaped, juxtalimbal corneal stroma associated with an epithelial defect, presence of stromal inflammatory cells, and stromal degradation.
  - Conjunctival, episcleral, and scleral inflammation are usually evident
  - Up to 50% related to systemic disorders
  - May progressive circumferentially to involve entire cornea
  - May progress to corneal melt syndrome leading to perforation

What is the Pathogenesis?

The peripheral cornea is adjacent to the vascularized posterior limbus .

Capillary arcades extend 0.5mm into clear cornea

The peripheral cornea and nearby limbus are unique in their cellular milieu

Peripheral Cornea has more Langerhans' cells, higher concentrations of IgM, and complement (C1)

What is the Pathogenesis

Antigen-presenting cells that express class II MHC antigens are capable of mobilization and induction of T cell responses.

Circulating immune cells, immune complexes, and complement factors tend to deposit adjacent to the terminal capillary loops of the limbal vascular arcades

They produce collagenase. Vasculitic processes also cause damage to vessel walls

This produces a variety of immune phenomena that manifest in the peripheral cornea

Common systemic causes

- Collagen vascular diseases/vasculitides are responsible for approximately one half of noninfectious cases of PUK

1. Rheumatoid Arthritis
    1. Most common cause
    - Painless guttering or acute painful ulceration
    - In patients studied by Tauber et al, RA accounted for 34% of noninfectious PUK
    - Patients with destructive PUK and necrotizing scleritis have a decreased life expectancy because of systemic vasculitis

2. Wegener's Granulomatosis (ANCA-associated granulomatous vasculitis or Granulomatosis with polyangiitis)
    1. Upper/Lower Respiratory tract, urinary tract
    - 60% have ocular involvement, most commonly PUK
    - Often bilateral manifestation with this disease
    - C-ANCA important

Common Systemic Causes

3. Polyarteritis Nodosa
   - A wide variety of ocular manifestations can be seen in 10% to 20%
   - Case reports of PAN presenting with PUK

4. Systemic Lupus Erythematosis
   - Corneal manifestations are confined mainly to the epithelium, and keratoconjunctivitis sicca is the most frequent corneal involvement
   - SLE is a relatively rare cause of PUK

5. Relapsing Polychondritis
   - rare autoimmune disorder characterized by a recurrent inflammation of the cartilaginous tissues throughout the body, particularly the ears and nose
   - Ocular inflammation is common and has been estimated to occur in up to 60% of patients
   - 4% of ocular manifestation is PUK

Topical Management

1) Improved lubrication
   - Many RA pt's have concomitant sicca syndrome
   - Lubrication may aid in diluting the effect of inflammatory cytokines in the preocular tear film
2) Promoting Re-epithelialization
   - Aid in slowing or stopping melting
   - May consider patching, bandage contact lens
3) Suppressing the systemic-mediated inflammation
   - Topical corticosteroids inhibit collagenase function
   - Suppress corneal inflammation, but may delay re-epithelialization, pre-dispose to superinfection, or worsen melting by suppressing collagen production

Other Treatment

1. Rule out infectious etiology with appropriate cultures

Mild: In milder, unilateral cases of peripheral ulcerative keratitis (and typically when not associated with a systemic CVD), topical corticosteroids may be considered as initial therapy

Moderate: Systemic corticosteroids, in the form of oral prednisone 1 mg/kg/day, are very commonly used in conjunction with topical corticosteroids for the acute management of more severe cases of PUK.

Severe: therapy is directed at controlling the inflammation with systemic corticosteroids at doses up to 100 mg/day combined with immunosuppressive agents. The presence of vasculitis is also a key factor in deciding if systemic immunosuppressive therapy will be required with concurrent associated scleritis highly suggestive of an active vasculitis process.

Indications for Systemic Immunomodulatory Therapy in PUK

1. PUK associated with a potentially lethal systemic disease, such as rheumatoid arthritis, Wegener's granulomatosis, relapsing polychondritis, polyarteritis nodosa
2. PUK with associated scleritis
3. Bilateral Mooren's ulcer
4. Disease progression despite local conjunctival resection and tectonic procedures (e.g., tissue adhesive)

IMMUNOMODULATORY/IMMUNOSUPPRESSIVE THERAPY IN PUK

Drug	Disease Indication	Dosage	
Azathioprine	RA, WG and RP (2^{nd} choice)		Bone Marrow Suppression
Cyclophosphamide	WG and PAN (1^{st} choice), RA (severe), RP (2^{nd} choice)	2mg/kg/day	Hemorrhagic Cystitis
Methotrexate	RA (1^{st} choice), maintanance for WG	10–25mg/wk PO or SubQ	Ulcerative Stomatitis, leukopenia, nausea, and abdominal distress
Cyclosporin A	Idiopathic (1^{st} choice), RA, RP (2^{nd} choice)		renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.
Rituximab/Infliximab	RA, Crohns		Fever, chills, asthenia, headache, and abdominal pain

Recurring Theme

Rituximab for peripheral ulcerative keratitis with Wegener Granulomatosis

- Cornea. 2010 Jun;29(6):708-10.

Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up.

- Cornea. 2009 Jan;28(1):89-92.

Infliximab for severe peripheral ulcerative keratopathy revealing Crohn's disease.

- Inflamm Bowel Dis. 2011 Mar;17(3):866-7

Rituximab in rheumatoid arthritis-associated peripheral ulcerative keratitis

- Arch Soc Esp Oftalmol. 2011;86:118-20. - vol.86 núm 04

Infliximab for progressive peripheral ulcerative keratitis in a patient with juvenile rheumatoid arthritis

- Jpn J Ophthalmol. 2011 Jan;55(1):70-1. Epub 2011 Feb 18.

Surgical Options

- conjunctival resection/biopsy
- cyanoacrylate adhesive
- conjunctival flaps*
- amniotic membrane grafts
- tectonic lamellar graft
- penetrating corneal grafts
- Patch grafting

***typically palliative since alone they do not influence the underlying immunologic process
***grafts are also susceptible to melting

Mooren's Ulcer

TYPES

1) Unilateral, less painful, presentation in older population with equal sex distribution, idiopathic
2) Bilateral, rapidly, painful progressive form in West African males

- Cause is unknown by definition
- Chronic, progressive ulceration
- Incidence is high in areas where parasitic infections are endemic
  - Theory involves previous infection resulting in autoantibodies
- Typically begins nasally or temporally and spreads circumferentially, then centripetally
- Type II hypersensitivity
- Associated with Hep. C, Crohn's disease, and Hydradenitis

PUK vs. Mooren's Ulcer

- Mooren's ulceration may be difficult to distinguish from PUK associated with collagen vascular disease.

- Signs/Symptoms of Mooren's include
  - extreme ocular pain
  - absence of scleral involvement (purely corneal involvement)
  - typical overhanging central corneal edge
  - lack of associated systemic findings

Prognosis of PUK

- The course, duration, and outcome are variable
- Dependent on the underlying cause of the PUK and on prompt and appropriate management.
- The prognosis is more guarded when PUK is associated with a systemic CVD.
- Significant visual loss and ocular morbidity may develop with corneal perforation.
- Many patients with mild or moderate PUK may maintain good vision if the inflammatory process is rapidly controlled.
- Both ocular and systemic prognosis is more guarded when there is concomitant scleritis, especially necrotizing scleritis.
- In up to 25% of cases, a systemic disorder is recognized after the presentation of the eye disease..

Patient follow-up

- Patient followed up in clinic two times since initial presentation
  - Started on Pred Forte q2
- Symptoms improved each visit
- Clinical improvement was noted at each visit
- Patient was called multiple times to stress importance of follow-up
- Patient referred to Rheumatology, pending

Patient follow up

- Labs
  - CBC wnl
  - ANA: 12 (negative)
  - ESR: 10 (wnl)
  - ANCA: 15 (negative)
  - RF: <7.0 (wnl)
  - Treponemal IgG: reactive
    - RPR: non-reactive

Reflective Practice

This case demonstrated the importance of maintaining correspondence with patients who may not fully understand the seriousness of their condition as symptoms improve.

Providing the appropriate level of explanation of the patient's disease allow the patient to better understand and comprehend their disease possibly leading to better compliance with treatment

Core Compentencies

- Patient Care: The case involved thorough patient care and workup of a broad differential diagnosis. Everything was done to treat the patient appropriately for the cause of his problem
- Medical Knowledge This presentation allowed us to review the common and unique causes of peripheral ulcerative keratitis as well as the broad range of treatments associated with each
- Practice-Based Learning and Improvement: This presentation included a current literature search of developing associations and current treatment modalities
- Interpersonal and Communication Skills: The patient was treated with respect and every effort was made to communicate in the patients primary language to facilitate better communication between the patient and team. The patient was also followed up with to urge continued treatment
- Professionalism: The patient was treated in the manner that allowed his disease process to resolve quickly. Other areas of concern were addressed in order to send patient to the correct specialist.
- Systems-Based Practice: The patient was worked up thoroughly for other possible systemic causes for his disease. An appropriate history was taken to facilitate this process.

References:

- Images: Images: Matthew Swanic, MD; Michael B. Raizman, MD*Am Fam Physician*. 2002 Sep 15;66(6):991-998.
- BCSC: External Disease and Cornea. Ch. 7 pg 210-220
- Yanoff & Duker: Ophthalmology, 3rd ed. Ch. 4.16
- Scleritis and Peripheral Ulcerative Keratitis. Anat Galor, MD1 and Jennifer E. Thorne, MD, PhD1,2. *Rheum Dis Clin North Am. 2007 November ; 33(4): 835–854.*
- Vasculitic Peripheral Ulcerative Keratitis. ELISABETH M. MESSMER, MD, 1 AND C. STEPHEN FOSTER, MD 2 Surv of Opth Vol 43.5 March-April.1999

Thank you

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