Clinical Challenges in Uveitis: Trouble in Paradise!

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• Lecture Bureau for:
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• No animals were harmed or mistreated in the development of this lecture

OVERVIEW OF UVEITIC DISEASE
• Classification
• Immune Response
• Laboratory Evaluation
• Treatment Philosophies
• Management
Overview of Immune Response in Uveitis – so simple even a Caveman could understand it!!!!!!

1. Presentation of ocular antigen to T lymphocyte
2. Activation and clonal expansion (CD 4 & 8 ^)
3. Activated Uveogenic T Cells AND circulating leukocytes come to eye
4. Migration into eye with initial breakdown of Blood / Ocular barrier.
5. Mast cell degranulation and inflammation amplification.

UVEITIS WORK-UP

• History - vital component
  - Unilateral or bilateral presentation
  - Time course
  - Prior therapy
  - Systemic diseases - (i.e., Sarcoidosis, Herpes simplex, Herpes zoster)
  - STD's - (i.e. AIDS, syphilis, chlamydia)

- Diet - (i.e. Toxoplasmosis)
- Pets - (i.e. Toxoplasmosis, Toxocariasis)
- IV drug use - (i.e. fungal)
- Family history

- Age
- Race
- Sex
- Geographic location (Ohio / Mississippi / Missouri)
- Symptoms - (i.e. photophobia, pain, redness, decreased vision, lacrimation, etc.)
Best Three Questions to ask and Document in Patient with Uveitis

1. Recent Skin Rashes: Sarcoid, Reiter's, Bechet’s, Psoriatic Arthritis.
2. Recent Respiratory Problems: Sarcoid, Histo, Coccidiomycosis, TB
3. Recent Joint Pain or Stiffness: Anklyosing Spondylitis, Reiter’s, IBD, Psoriatic Arthritis.

“Suggested” office work up

- Physical observation peri-ocular tissues
- Pupils
- Biomicroscopy
  - Endothel. (KPs) type, configuration.
  - A/C
  - Iris--look for nodules, PS, AS
  - Ant. Vitreous
- BIO and Extended Ophthalm. (R/o Post. Uveitis)
- IOP
- Charges (99214 or 99204)

Lab work-up

- First time attack- no signs & suggestive Hx. (none or minimal)
- Referral letter to M.D.
- If possible - order a few tests if uveitis is recurrent/severe
- Things to ponder:
  - 50% labs come up negative
  - Should be 50% certain of the disease in chair to direct lab test

Treatment Philosophies
**Steroids**

- Need a long acting steroid with good anti-inflammatory properties (Pred. Forte 1%, Lotemax, Durezol - good choices)
- Need to use the steroid aggressively in the first 10 to 14 days (q1h or q2h) - you have no idea what level the inflammation is at.
- If AC cells drop from one grade to a lower grade (3+ → 2+), continue with frequency of (q1h or q2h), wait for significant reduction to “taper”

**New Steroid**

- Never (?) switch steroids if Tx. is working but IOP elevates - uveitis patients are steroid responders too.
- Always evaluate IOP at every visit as well as corneal to R/o HS
- Taper steroid from q1h to q2h when cells have significantly reduced or minimal AC rxn before you start to taper. Inflammation does way more damage than IOP.

**Cycloplegia**

- Good for the first 3 days to reduce photophobia, PS/PAS, and help shore up blood/ocular barrier
- If no synechiae are present D/C after 3 days
- If synchiae already there - may need to keep patient on cyclo. Tx. or if fibrin level is high in AC
- If multiple synechiae present - try atropine/scopolamine/10% Neosynepherine to break synechiae and consider longer duration cycloplegics if synechiae are 180° or greater and IOP is elevating
Few Items

• Steroids cause ptosis (1-2mm) - it goes away after D/C steroid
• Steroids cause mydriasis - it goes away after D/C steroid
• Steroids alters TBUT, corneal rigidity, tear production - returns to normal after D/C steroid
• Pressure usually goes up 10 mmHg for steroid responder (30% max. with exceptions)
• Secondary glaucoma - most handled with topical therapy, some require surgical intervention
• Two types of glaucoma: Pupillary Block Glaucoma versus secondary steroid induced / AACG (PAS)

Take Home Pearl:

• In an effort to do no harm with a topical steroid, practitioners utilize steroids sparingly causing greater harm to the eye in the long run

Future for biological therapy for uveitis

• Include AB’s, soluble receptors, and cytokines
• Anti-TNF alpha- most widely employed*
• IntraVitreal Injections (Anti-Inflam. & nano)
• Biologics have tremendous potential in the treatment of ocular inflammation but studies have been limited and side-effects are not completely known.**

New and Standard Treatment Modalities

Antimetabolites
- Azathioprine (Imuran)
- Methotrexate (Rheumatrex)
- Mycophenolate Mofetil (Cellcept)
- T-Cell Inhibitors
- Cyclosporine (Sandimmune, Neoral)
- Tacrolimus (Prograf)
- Alkylating Agents
- Chlorambucil (Leukeran)
- Cyclophosphamide (Cytoxan)

Biologics
- Infliximab (Remicade) **
- Etanercept (Enbrel)
- Interferon (Avonex)
- Daclizumab (Zenapax)
- Alefacept (Amevive)
- Efitizumab (Raptiva)


A protein produced by molecular recombinant DNA technology and designed to have a therapeutic effect on the inflammation based on current understanding of the disease pathogenesis.
Key Features in Uveitis Treatment
• Topical steroids are the mainstay of therapy for acute iridocyclitis
• Systemic corticosteroids are beneficial for bilateral, non-infectious, endogenous uveitis (avoidance of chronic use due to complications)
• Newer classes of immunomodulatory agents currently are: anti-metabolites, calcineurin inhibitors, alkylating agents and biologics.
• Determination of an immunosuppressive regimen requires a careful assessment of the benefits and risks of therapy

NSAIDS that can be utilized with AU
• Fenoprofen Nalfon
• Ketoprofen Oridus
• Piroxicam Feldene
• Flurbiprofen Ansaid
• Ketorolac Toradol
• Naproxen Naprosyn
• Ibuprofen Motrin, Rufen

Top Causes / Associations of Anterior Uveitis
• Idiopathic (AKA: Undifferentiated)
• HLA- B27 related (CRAP)
• Sarcoidosis
• Herpes Virus (HSV & VZV)
• Juvenile Idiopathic arthritis – associated uveitis
• Fuch’s Heterochromic Iridocyclitis (FHI)
• Posner-Schlossman Syndrome
• Syphilis
• Masquerade Syndrome

DIFFERENTIAL DIAGNOSIS AND TREATMENT OF UVEITIS
• Anklyosing Spondylitis
  – Etiology
    • Disease of the axial skeleton
    • Males (3x) > females (1x)
    • Ages 20-40
    • Women – older and more
      – Peripheral joint involvement.
      – Neck pain and breast pain

• Affects 0.1% of Caucasian adults
  - Lower back pain in morning lasting 15 min. > 3 months
  - Other complaints are “pain in the chest cavity and difficulty with chest expansion”
  - anorexia, fever, malaise - systemic signs

• Ocular presentation
  - Anterior uveitis - usually unilateral
  - Recurrence in same or other eye
  - Rapid onset of pain and photophobia
  - Flare may be heavy or light
  - Posterior synechiae form quickly
  - Episodes vary 2-6 weeks
Fibrin clots or aggregations

Investigations

• X-ray of sacroiliac joints
• (MRI for early enthesopathy if X-rays negative----enthesopathies are disorders of peripheral ligamentous or muscular attachments)
• ESR ↑ / C-reactive protein ↑
• RF (-) / ANA (-)
• Family Hx of AS
• Alkaline phosphotase levels ↑
• HLA B27 (+) tissue typing
• Vitamin D Levels -Risk of Osteoporosis
• Electrocardiogram (??) if heart Dz in the FH
Ocular / Systemic Therapy

- Topical steroids (q1h to q2h - initially)
- Topical cycloplegic agents (QD or BID)
- Periocular steroid injections for more severe cases
- NSAIDS, COX-2 inhibitors - main stay for systemic treatment & physical therapy
- TNF inhibitors (Etanercept, Infliximab)

Can't see. Can't pee, Can't Dance with Me

- Reiter's Syndrome (Reactive Arthritis)
  - Etiology
    - Triad (conjunctivitis, arthritis, urethritis)
    - Anterior Uveitis in 15 to 20%
    - Males > females (9:1 / 1:1)
    - Ages 18 - 40 more common

Forms of RS

- Post venereal = conjunctivitis (30-60%)
- Arthritis (asymmetric- large weight bearing joints) presenting with anterior uveitis (15%)
- Post dysenteric: Shigella, Yersinia, Salmonella, Campylobacter - (usually 1 to 4 weeks after the dysentery)
- Chlamydia Trachomatis, most common agent causing the venereal disorder so look for signs of inclusion conjunctivitis or Ureaplasma urealyticum

Ocular presentation / Systemic signs

- Inclusion conjunctivitis is most common presentation → post infection (2-4 wks → uveitis)
- Superior micropannus of cornea (if chlamydial infection)
- Anterior uveitis → arthritic form
- Systemic signs with ocular presentation: keratodermal blennorrhagicum, circinata blanatis (ddx: pustular psoriasis), aphthous stomatitis, rheumatologic signs: plantar fasciitis.
Keratoderma Blennorrhagicum
Balanitis circinata
Aphthous Ulcers

• Heavy flare and cells (flare may be plasmoid)
• Course is 2-6 weeks
• Glaucoma possible after repeated episodes

Investigation
• X-rays of knees, ankles, feet, heels, Achilles tendon, and sacroiliac area
• Cultures for chlamydia from conjunctiva, urethra
• HLA-B27 (++)
• Fecal cultures for post dysenteric
• ESR and CBC (leukocytosis with mild anemia ?)
• Creatinine – Elevated
Investigation

- Nail pitting
- Palate / tongue ulcers
- HLA tissue typing (HLA B27)
- RF (-)
- ANA (-)

Ocular / Systemic Treatment

- Topical steroids (Q1h to Q2h initially)
- Quick removal of steroids may cause return of inflammation
- Topical cycloplegics (QD to BID)
- Periocular steroid injections for more severe cases
- NSAIDs, second line: methotrexate & sulfasalazine
- Co-management with interest for venereal; rheumatologist for arthritis is recommended

Systemic therapy (if venereal)

- Oral tetracycline 250mg
- Oral doxycycline 100 mg
- Oral arithromycin 1000 mg (zithromax)
**Sarcoidosis**

- **Etiology**
  - Usually African-American (blacks 8-10X > whites)
  - Also Euro Whites / Japanese patients
  - Women = men
  - Multi-systemic disease: hallmark, non-caseating granulomas (eval. the peri-ocular region)
  - Accounts for 3-10% of all uveitic cases
  - 50% patients develop ocular sequellae – usually anterior
  - Etiology unknown – immunological pathology

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**Ocular Presentation**

- Bilateral iridocyclitis
- Dense posterior synechiae
- Mild pain and photophobia
- Palpebral conjunctival may manifest sarcoid granulomas (17%)
- Lacrimal gland enlargement

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- Most commonly seen in the Atlantic Gulf Coast states
- Ages 20-40 (children under age 5) 60 to 70
- Disease has anterior and posterior involvement
- Acute / chronic presentation
- Systemic symptoms: respiratory (most common symptom) associated with fever, fatigue (27%), dyspnea, weight loss (28%)
- Patients may be asymptomatic at the time of Dx.
• KP's are extremely large (mutton-fat)
• Iris nodules are usually present (20%)
• Cataracts and glaucoma are complications (chronic form)

• Posterior segment: (involvement is less frequent)
  - Vitreous snowballs - located inferiorly and lie on the retinal surface (vitritis)
  - "Candle wax drippings" - (en taches de bougie) venule involvement
  - Perivenous sheathing
  - Choroidal lesions (Dalen-Fuch's nodules)
- Choroidal granuloma (rare)
- Chronic cystoid macular edema
- Neovascularization of the disc (15%)
- Optic disc swelling (40%)

Skin lesions - erythema nodosum or sarcoid nodules under the skin
Lungs are frequently affected
Facial nerve palsies are possible as well

Investigations

- Chest X-ray (hilar adenopathy) Lung is the number one organ affected by the disease
- ACE (+) >67U/L
- Serum lysozyme (+)
- PPD (-)
- Blood panel

May present as:
- Shortness of breath
- Chest pain
- Persistent dry cough
• Gallium scan of the head and neck
• Biopsy of conjunctiva or skin or lacrimal gland nodule
• ACE and gallium scan will give false negative if patient is taking steroids
• Pulmonary function tests

Differential diagnosis

• Sickle cell disease
• Lyme Disease
• TB
• Idiopathic pars planitis
• Histoplasmosis / Coccidioidomycosis

Systemic Treatment
1. Spontaneous resolution in 24-36 months (50%)
2. Low dose Corticosteroids (20-40 mg/d)
3. Cyclosporin therapy - no safe long term approach with this drug
4. Methotrexate--low dose good for long term tx (azathioprine)
5. Chloroquine (Hydrochloroquine) for pulmonary
6. Biologics (Entanercept / Infliximab for refractory uveitis)

Ocular Treatment

• Topical steroids (q1h to q2h) depends on activity
• Topical cycloplegics (BID or QD)
• Periocular steroids if topicals are ineffective (intermediate)
• Oral steroids and histamine H2 blocker if treating intermediate / posterior uveitis, facial nerve palsies, pulmonary problems
• Cyclosporin A - effective in patients intolerant to oral steroids
• Anti-glaucoma meds (topical and oral) for 2° complications (aqueous suppressants)
• Panretinal photocoagulation for neovascularization
• Patients need to be re-examined in 3-7 days
• Asymptomatic patients seen Q 6 months
• Steroid treated patients need to be seen Q 3 months
• Children with Sarcoidosis need to be seen Q 1-3 months

Thank you for taking the course!