Underlying Systemic Conditions for Anterior Uveitis

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Outline

- Classification
  - Anatomy
  - Clinical course
  - Histopathology
  - Etiology
- Specific Conditions
  - Non-infectious
  - Infectious
  - Other

CLASSIFICATION

Classification Based on...

- Anatomy
  - what part of the uveal tract is affected
- Clinical Course
  - Acute
  - Chronic
  - Recurrent
- Etiology
  - Infectious
  - Noninfectious
  - Masquerades
- Histopathology
  - Granulomatous
  - Nongranulomatous

International Uveitis Study Group (IUSG) in 1987

- Developed a universally accepted classification system for Uveitis
- Based on anatomical location of the inflammation

Why Localize the Inflammatory Process?

- The anatomical location of the inflammatory process is one of the most important clues to pathogenesis and treatment
  - Anterior
  - Intermediate
  - Posterior
  - Panuveitis
Anterior Uveitis

- Primary site of Inflammation= **anterior segment**.
- Most common form of intraocular inflammation (50-90%)
  - Iritis
  - Iridocyclitis
  - Anterior cyclitis
- Sometimes anterior vitreous cells (called spillover uveitis) may occur
  - Cells from the anterior chamber spilling over to the vitreous
  - Anterior is still the primary source of disease

2 Sub-classes of Anterior Uveitis: Differ in **Histopathophysiology**

Granulomatous

- May result from an autoimmune reaction or from the host's immune response to a systemic infectious process
  - Syphilis
  - Lyme disease
  - Tuberculosis (TB)
  - Local reactivation of herpetic viral infection.

Non-granulomatous

- Inflammation of the iris and the ciliary body causes a breakdown of the blood ocular barrier.
- This condition allows both protein and WBCs to extravagate into the aqueous, resulting in the typical iritis signs of cell and flare.
- Typically, but not always, non-infectious

Granulomatous Inflammation

- An inflammatory manifestation of infectious, toxic, allergic, autoimmune and neoplastic origin.
- Characterized by inflammatory cells of the mononuclear phagocyte system that take the form of:
  1. Macrophages
  2. Epithelial cells
  3. Multinucleated giant cells
- Can be an indicator of Chronic Inflammation too!

Intermediate Uveitis

- Primary site of inflammation = **Vitreous**
  - posterior cyclitis, hyalitis, choroiditis, and chorioretinitis.
  - Vitritis or vitreous cells: common sign
- Pars planitis
  - subset of intermediate uveitis
    - snowbank or snowball formation occurring in the absence of an associated infection or systemic disease.

Intermediate Uveitis

- Associated with:
  - Infection (eg, Lyme disease)
  - Systemic disease (eg, sarcoidosis)
  - Granulomatous diseases (eg, tuberculosis, sarcoidosis, Lyme disease, syphilis).

Posterior Uveitis

- Primary site of inflammation: **choroid and the retina**
  - Retinochoroiditis
  - Retinitis
  - Neuroretinitis
Panuveitis

- The term panuveitis is reserved for those situations in which there is no predominant site of inflammation
  - Inflammation in the
    - anterior chamber
    - vitreous
    - retina and/or choroid

Summary Anatomical Classification

- anterior uveitis (iritis, iridocyclitis, and anterior cyclitis)
- intermediate uveitis (para planitis, posterior cyclitis, and hyalitis)
- posterior uveitis (focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis)
- panuveitis (anterior chamber, vitreous, retina, and choroid)

Standardization of Uveitis Nomenclature (SUN) Working Group in 2005

- Standardized the methods for reporting clinical data (diagnostic terminology, inflammation grading schema, and outcome measures) for uveitis
- A standardized grading for clinical signs of intraocular inflammation
  - anterior chamber cells
  - anterior chamber flare
  - vitreous cells
- Standardized definitions of outcomes, including reporting visual acuity outcomes, were approved for research.

SUN Descriptor of Uveitis

- Onset
- Duration
- Course

Onset

- The onset described as sudden or insidious based on history.
  - Sudden
    • Symptoms and clinical signs “suddenly” appear
  - Insidious
    • Slow gradual development of symptoms, signs
    • Sometimes patients are only mildly symptomatic

Duration

- The duration of an attack of uveitis:
  - Limited
    • ≤ 3 months in duration
  - Persistent
    • > 3 months in duration.
Clinical **Course of the Uveitis**

- **Acute** describes the course of specific uveitic syndromes characterized by sudden onset and limited duration.
  - Lasts <3 months
- **Chronic** describes persistent duration with relapse <3 month after discontinuation of therapy.
  - Last >3 months
- **Recurrent** describes repeated acute episodes separated by periods of inactivity without treatment > 3 months in duration.

**International Uveitis Study Group (IUSG) in 2009**

- Designed a simplified, clinical classification system for uveitis based on etiological criteria.
  - 3 main categories:
    - **infectious** (eg, bacterial, viral, fungal, parasitic)
    - **noninfectious** (eg, known systemic associations, no known systemic associations)
    - **masquerade** (eg, neoplastic, non-neoplastic).

**What Causes Uveitis?**

**Based on the International Uveitis Study Group (IUSG) Clinical Classification of Uveitis**

- **Non-infectious**
- **Infectious**
  - Bacterial
  - Viral
  - Fungal
  - Parasitic
  - Others
- **Masquerade** (Neoplastic vs. Non-neoplastic)
  - Intraocular cells not due to immune mediated uveitis

**Presentation Points**

- The condition
- Signs, symptoms, etiology
- The type of uveitis
  - Acute, chronic, recurrent
  - Granulomatous vs non-gran
- The typical work-up
  - Labs
- Referrals
- Who to best manage the systemic disease
- Treatment
  - Systemic
  - Ocular

**Non-Infectious Etiologies**

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>PLA-B27</td>
<td>Auto-immune Disease</td>
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<tr>
<td>Ankylosing Spondylitis</td>
<td>Lupus</td>
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<tr>
<td>Reiter’s</td>
<td>Wegener’s</td>
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<tr>
<td>Inflammatory Bowel (Colitis, Crohn)</td>
<td>Polyarthritis</td>
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<tr>
<td>HLA-B27</td>
<td>Tuberous Sclerosis</td>
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<td>Chronic Uveitis Nephropathy</td>
<td>Fuch’s Heterochromia</td>
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<td>Glaucoma (Gouty)</td>
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<td>Gout</td>
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<td>Lens associated (phacolytic)</td>
<td>Bartter’s</td>
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<tr>
<td>Trauma and post-operative</td>
<td>Sarcoidosis</td>
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<td>Drug induced (Rababitt, Gatiflor)</td>
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**Infectious Uveitis**

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<thead>
<tr>
<th>Bacterial</th>
<th>Fungal</th>
<th>Parasitic</th>
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**Masquerades**

<table>
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<th>Non-Neoplastic</th>
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<tr>
<td>Retinitis Pigmentosa (RP)</td>
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<td>Ocular Ischemic Syndrome</td>
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<td>Chronic retinal detachment</td>
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<td>Intraocular FB</td>
<td>Uveal Melanoma</td>
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<td>Pigment dispersion syndrome (PDS)</td>
<td>Retinoblastoma</td>
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<td>Juvenile xanthogranuloma</td>
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<td>Metastatic Tumors</td>
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</table>

**Non-Infectious Etiologies**

- **Acute**
  - HLA-B27
  - Ankylosing Spondylitis
  - Rheumatoid Arthritis
  - Inflammatory Bowel (Colitis, Crohn)
  - Psoriatic Arthritis

- **Tubulointerstitial Nephritis**
  - Fuch's Heterochromia

- **Lens associated (phacolytic)**
  - Behcet's

- **Trauma and post-operative**
  - Sarcoidosis

- **Drug induced (Ribabutrin, Cidfovir)**
  - Juvenile Rheumatoid Arthritis (JRA)
  - Juvenile Idiopathic Arthritis (JIA)

- **Behcet's**
  - Vogt-Koyanagi Harada Disease (VKH)

- **Sarcoid**
  - Sympathetic Ophthalmia

- **Idiopathic**

**HLA-B27**

- Human cells and tissues contain surface markers that enable the body to differentiate its own cells from foreign material.
- Genotype located on the short arm of Chromosome 6.
- Present in 1.4-8.0% of population
- 50-60% of acute or recurrent anterior uveitis, may be HLA-B27 positive.
- Non-granulomatous
- Several autoimmune diseases collectively called seronegative spondylarthropathies (RF)
  - are strongly associated with both acute uveitis and HLA-B27.

**Most Common Non-Infectious Underlying Etiology for AU**

- 50% of acute anterior uveitis (AAU) test +HLA-B27
  - AND 50% of HLA-B27+ AAU will go on to develop one of the seronegative arthritides
    - CRAP
      - Chronic Inflammatory Bowel diseases
      - Reiter's Syndrome (Reactive Arthritis)
      - Ankylosing Spondylitis
      - Psoriatic Arthritis
  - 25% who have been dx with HLA-B27 arthritis will develop AAU
- Up to 70% of Caucasian pts with AAU are HLA-B27 positive
- 1st attack 20-40 yrs of age
- 10% suffer severe visual impairment or blindness
- Most commonly due to CME

**Typical Penotype of HLA-B27-positive AAU**

- Sudden onset
- Unilateral
  - Often alternating
  - Rarely bilateral
  - Reiter's the exception
- Non-granulomatous AAU
- More likely to have:
  - Iritis
    - hypopyon
  - Posterior Synechia
- High tendency for recurrences
- Significant association with other HLA-B27-related systemic diseases.
- Males more than females
Seronegative Spondyloarthropathies

- Ankylosing Spondylitis
- Reiter’s Syndrome (Reactive Arthritis)
- Chron’s/Inflammatory Bowel diseases
- Psoriatic Arthritis

Ankylosing Spondylitis (AS)

- Inflammatory arthropathy most frequently seen in males.
- Early symptoms include lower back pain and stiffness after inactivity (i.e., sleeping) that can progress to severe deformity of the lower back.

Si x-rays may show sclerosis and narrowing of the joint space.
Inflammation of the sacroiliac joints is the classic sign – the spinal column is also frequently involved.

The AS Stereotype?
- Young 20-30 yo
- 1% of population
- More in Caucasians
- Male (4:1)
- Acute non-granulomatous Anterior uveitis
- Lower back pain that improves with movement/exercise

What to do if You Suspect AS?
- Labs:
  - HLA-B27
  - ESR
    - But non-specific
- Imaging:
  - X-rays of the SI joints (poor imaging, but the standard)
  - CT or MRI of the SI joints (better, but more costly)
- Referral:
  - Rheumatologist

Reiter’s Syndrome
- Classic diagnostic triad:
  1. Arthritis-98%
  2. Urethritis -74%
  3. Conjunctivitis-58%
- Anterior Uveitis in 3-12%
- Etiology is thought to result from infection from Chlamydia, Ureaplasma urealyticum, Shigella, Salmonella, and Yersinia.
  - Arthritis begins within 30 days of infections?
    - Knees, ankles, feet, wrists

Infection and HLA-B27
- Non-infectious immune-mediated inflammation
  - Occurs after infections of the genitourinary or gastrointestinal tract.
  - Reiter’s/Reactive Arthritis
  - Chron’s
- Bacteria thought to be responsible:
  - Salmonella, Shigella, Campylobacter, Klebsiella, and Yersinia, or Chlamydia trachomatis,

How Does Bacteria Cause a Non-Infectious AAU?
- “uveitogenic” peptides from certain bacteria are bound and presented by HLA-B27 to T cells.
- These microbe-derived antigens may trigger CD8+ T-cell immune responses that cross-react with self-tissue antigens (molecular mimicry) that are uniquely found in the uvea or joint tissue, resulting in autoimmune tissue inflammation.

Other findings

- Keratoderma blennorrhagicum
- Circinate balanitis
- Plantar fasciitis
- Achilles tendonitis
- Sacroiliitis
- Nailbed pitting
- Palate ulcers
- Tongue ulcers

Reiter’s Uveitis

- Acute, chronic, or recurrent, non-granulomatous AU
- Often bilateral
- Male > females
- 20-40 yo
- Joint deformities
- Urethral discharge

What to Do if You Suspect Reiter’s?

- Labs:
  - HLA-B27 (+ 70-90%)
  - ESR is often elevated
- ROS:
  - Classic clinical signs
    1. Urethritis
    2. Arthritis
    3. Conjunctivitis (or Ant Uveitis)
- Referrals:
  - Urologist for urethral cultures, urine analysis
  - Rheumatologist for arthritis evaluation and possible imaging of the spine/joints

Inflammatory Bowel Disease

- Includes:
  - Ileo-Colitis (Crohn’s disease)
    - 2.4% will have anterior uveitis
  - Ulcerative Colitis
    - 5-12% will have anterior uveitis
- Symptoms include abdominal pain, diarrhea, weight loss, fever, fatigue, joint pain
- 20% will have sacroiliitis
- 60% will be HLA-B27 positive

What to Do if You Suspect Inflammatory Bowel Disease?

- Labs:
  - HLA-B27
- Referrals:
  - Internal Medicine
  - Gastroenterologist

Psoriatic Arthritis

- 7-25%
- acute, chronic, recurrent non-granulomatous anterior uveitis
- Psoriasis with arthritis
- Erythematous hyperkeratotic rash
- Tissue swelling, distal joint inflammation
- Nail bed pitting (ungual changes), discoloration, thickening, cracking, ridging
Psoriatic Arthritis

- Diagnosis made by cutaneous changes, terminal joint inflammation, ungual involvement
- Pts suffer with Conjunctivitis and anterior uveitis
- Psoriasis may precede arthritis by several yrs
- M = F
- 40-50 yo

What to do if You Suspect Psoriatic Arthritis?

- Labs:
  - HLA-B27
- Referrals:
  - Dermatologist
  - Rheumatologist

Ocular Treatment of the Uveitis of +HLA-B27

- Aggressive Topical Steroids
  - Dosing every hour (12-14x/day with pred acetate 1% vs Durezol 4-6x/day)
- Cycloplegics
- HLA-B27 AU recur and can be chronic
  - Recommended a 4 week treatment to lessen relapse
  - Occasionally need oral immunosuppressive agents
    - Salazopyrine and methotrexate reduce recurrence?
  - Properly educate patient
- Get systemic work-up
  - Appropriate referral to subspecialty
- We can make the diagnosis of an HLA-B27 related uveitis, but must rely on sub-specialty to confirm condition (ie: CRAP)
  - 50% of HLA-B27+ AAU will go on to develop one of the seronegative arthritis

Non-Infectious Etiologies

Acute Chronic

- HLA-B27
  - Ankylosing Spondylitis
  - Reiter’s
  - Inflammatory Bowel (Colitis, Crohn)
  - Psoriatic Arthritis
- Auto-immune Diseases
  - Lupus
  - Wegener’s
  - Polyarthritis
- Tubulointerstitial Nephritis
- Fuch’s Heterochromia
- Sarcoidosis
- Behcet’s
- Drug induced (Rabatrin, Cidlofor)
- Juvenile Rheumatoid Arthritis (JRA)
- Juvenile Idiopathic Arthritis (JIA)
- Sympathetic Ophthalmia

Sarcoidosis

- Multisystem granulomatous disease of unknown etiology
- Non-caseating granulomas form in multiple systems
  - composed of epitheloid and giant cells
  - Granulomas secrete ACE

- Most commonly characterized by:
  - bilateral hilar lymphadenopathy,
  - pulmonary infiltration
  - dermatological manifestations
- Ocular involvement in 15-50%:
  - Uveitis; Orbital, lid, conjunctival granulomas; dry eye

www.uveitis.org
Sarcoid Presentation

- Inflammation:
  - Chronic iritis in 3-10% of all uveitis cases
  - Uveitis may be acute, recurrent, or chronic
  - Posterior uveitis (choroiditis, retinitis), perivascularitis, optic neuritis
  - May be bilateral or unilateral
- Females slightly more than males
- 20-50 years of age, but may occur in children as well
- African American 10-20x more than Caucasians

You Suspect Sarcoid?

- Exam:
  - Careful evaluation of the conjunctiva and lacrimal glands looking for granulomas/nodules
  - Skin nodules of eyelid, adnexa and systemic
- Labs:
  - Elevated serum lysozyme, ACE levels
- Other:
  - Chest x-ray or CT
  - Gallium scan
  - Tissue biopsy (lungs, lymph nodes, skin nodules, liver, conjunctiva, lacrimal gland)
  - Pulmonary function tests
- Referrals:
  - Internal medicine
  - Pulmonologist
  - Ophthalmology for ocular nodule biopsy

Serum ACE Levels

- Combined use of ACE levels with gallium scans increased the diagnostic specificity in cases of clinically active systemic sarcoidosis from 83% to 99% when compared to ACE levels alone.

Serum Lysosome

- The sensitivity of lysozyme for predicting sarcoidosis was 79.1%, whereas that of serum angiotensin-converting enzyme (ACE) was 59.0%.
- Even in the cases without an elevated serum ACE level, a value of 72.1% was obtained.
- The serum lysozyme level demonstrated a significant tendency to increase with the number of organs involved (p < 0.01).
Treatment of Sarcoid

• **Systemic treatment:**
  – steroids are the mainstay
  – NSAIDs may offer some benefit
  – Immunosuppressant agents
    • methotrexate, cyclosporine, and azathioprine

• **Ocular treatment of uveitis:**
  – Topical steroids, cycloplegics
  – Due to chronic and recurrent nature, high risk of steroid complication
  • Cataract, GLC

Non-Infectious Etiologies

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<tr>
<td>HLA-B27</td>
<td>Autoimmune Diseases</td>
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<tr>
<td>Felty’s Syndrome</td>
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<td>Glaucomatocyclitic Crisis</td>
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<td>Sarcoid</td>
<td>Sympathetic Ophthalmia</td>
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<td>Idiopathic</td>
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Various “Types” of Lupus

1. Systemic Lupus Erythematous (SLE)
2. Lupus Anti-coagulant (LAC) & Anti-Phospholipid Antibody (APL)
3. Neonatal Lupus
4. Drug-induced Lupus
5. DISC Lupus Erythematous (DLE)
6. Subacute Cutaneous Lupus Erythematous (SCLE)


Systemic Lupus Erythematous (SLE)

• Autoimmune, connective tissue disorder with multi-system involvement
  – characterized by the production of antibodies to components of the cell nucleus.
• Onset is primarily women of childbearing age
• Higher incidence among African Americans and Hispanics in the US.
• Most severe and widespread form of Lupus

Systemic Lupus Erythematous (SLE)

• Cause is unknown
  – thought to be due to overproduction of autoantibodies:
    • B-lymphocyte hyperactivity
    • polyclonal B-lymphocyte activation
    • Hypergammaglobulinemia
    • autoantibody formation
    • T-lymphocyte autoreactivity with immune complex deposition leading to end-organ damage.
• The clinical course is marked by spontaneous remissions and relapses
Clinical presentation:
- young female who presents with a viral or flu-type syndrome triggered by environmental factors with a photosensitive skin rash.
- chronic inflammatory autoimmune disease which can affect any organ system, but mainly involves the skin, joints, kidneys and nervous system.

Diagnosis of Lupus Requires 4 of 11
1. Macular Rash
2. Discoid Rash
3. Photosensitivity
4. Mucosal Ulcers
5. Arthritis
6. Serositis (pleuritis, pericarditis)
7. Renal Disorder
8. Neurological Disorder
9. Hematologic Disorder
10. Immunologic Disorder
11. Antinuclear antibody

“MD SOAP BRAIN”

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<th>M</th>
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<tbody>
<tr>
<td>D</td>
<td>Discoid Rash</td>
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<tr>
<td>S</td>
<td>Serositis, pleuritis, pericarditis</td>
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<td>O</td>
<td>Oral Ulcers, vasculopathy</td>
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<td>N</td>
<td>11. Neurologic: encephalopathy</td>
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Treatment of SLE
- No Cure. Goal is to control symptoms
  - Oral NSAIDs
  - Oral Steroids
  - Antimalarial drugs
    - Plaquenil
    - hydroxychloroquine
  - Immunosuppressive agents
    - Methotrexate
    - Imuran
    - Azathioprine

Often a Multisystem Consultation
- Rheumatologist
- Infectious disease specialist
- Neurologist
- Pulmonologist
- Cardiologist
- Gastroenterologist
- Nephrologist
- Dermatologist
- Hematologist

Ocular Complications with SLE
- Anterior Segment
  - Uveitis, episcleritis, scleritis, k-sicca
- Posterior
  - Lupus Retinopathy, papillitis, neuro-ophthalmic disease, vaculitis
Diagnosis

- 11 Diagnostic Criterion
- Labs:
  - ANA
    - Non-specific and can be positive in other conditions
  - Antibodies to dsDNA
  - Smith antigen

INFECTION ETIOLOGIES

Infectious Uveitis

- In patients you suspect have an infectious etiology, caution with steroid treatment, especially systemic steroid treatment.

WHAT IS ONE OF THE SIDE EFFECTS OF STEROIDS?

- Should treat the underlying infection either first or in conjunction with steroids.
- Rely on lab studies, history, ROS, and the presence of granulomatous uveitis, posterior segment involvement

<table>
<thead>
<tr>
<th>Infectious Uveitis</th>
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<th>Fungal</th>
<th>Parasitic</th>
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<td>Lyme Disease</td>
<td>Cytomegalovirus (CMV)</td>
<td>Aspergillosis</td>
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<td>Ocular necroticosis</td>
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<tr>
<td>Bartonella henselae</td>
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<td>Mononucleosis</td>
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<tr>
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</tbody>
</table>

Syphilis

- Syphilis is a multisystem, chronic bacterial infection caused by the spirochete Treponema pallidum

- It is associated with multiple ocular manifestations that occur in both the acquired and congenital forms

- Transmission occurs via sexual contact or transplacental
CDC Primary and Secondary Syphilis

- In US
  - 2000: 2.1 cases per 100,000
  - 2011: 4.5 per 100,000
  - 2013: 5.3 per 100,000
- In Illinois (ranked 9th of 50 States)
  - 6.2 per 100,000
- In CA (2nd)
  - 9.3 per 100,000
- Georgia (1st)
  - 10.3 per 100,000
- District of Columbia
  - 26.6 per 100,000
- Wyoming (50th)
  - 0.2 per 100,000

2013 Syphilis Rates

Syphilis

- Accounts for 1-2% of uveitis cases, but is considered the great masquerader
- Three stages of infections:
  - Primary, secondary, latent progressing to tertiary

Primary Syphilis

- After T. pallidum penetrates the skin or mucous membrane, the organism enters the lymphatics and blood stream and disseminates shortly after contact.
- If left untreated, primary syphilis leads to secondary syphilis

Secondary Syphilis

- The systemic treponemal load is largest in secondary syphilis.
- Generalized maculopapular (or pustular rash), and lymphadenopathy are the characteristic lesions in this stage.
- These lesions appear 4-10 weeks after the initial manifestation.
Secondary Syphilis

• Constitutional symptoms of fever, malaise, headache, nausea, anorexia, and joint pains often are present.

• The liver, kidneys, and/or GI tract may or may not be involved.

• Ocular involvement has been reported in 10% of cases, and cerebrospinal fluid (CSF) pleocytosis has been seen in a few cases.

Latent Syphilis

• Early Latent
  – occur within 1 year after initial infection,

• Late Latent
  – After 1 year of the initial infection

• Most cases have been reported to stay at the latent stage with 30% converting to the tertiary stage.

Tertiary Syphilis

• 3 sub-groups:
  – Benign tertiary
    • presents with gummatous lesions that are actually granulomas histologically; in the skin and the mucous membranes, the choroid, ciliary body, and iris
  – Cardiovascular
    • presents with involvement of the coronary arteries or the aorta.
  – Neurosyphilis
    • Manifest with tabes dorsalis or general paresis
    • CNS is affected via the vascular pathways or via direct involvement of parenchyma.

Ocular Syphilis

• Rarely occurs before 6 months after the primary infections

• Most ocular involvement occurs during the secondary, Latent or tertiary stages

• Uveitis may be acute, chronic or recurrent
  – Usually granulomatous, but may also be non-granulomatous

Making the Diagnosis

• Labs:
  – Non-treponemal serology tests
    • RPR or VDRL
      – Are antibodies present for treponema pallidum?
      – Indicate disease activity by quantifying amount of anticardiolipin antibody in serum
    • Reactive or nonreactive at dilutions of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, etc.
    • 50-75% can be nonreactive in early primary syphilis (<3 wks) • 100% reactive 4+ weeks after exposure, secondary, early latent
      • Can be negative in late syphilis
      • Most often used as a screening test

• Labs:
  – Treponemal serology tests
    • FTA-ABS or MHA-TP
      – Reactive or nonreactive
    • Will test positive after primary infection indicating either active or past infection

• Referrals:
  – Internal medicine and/or infectious disease
Treatment for Syphilitic Uveitis

- Must determine what stage the infection is in before determining treatment:
  - Congenital: IV penicillin
  - Primary, secondary, or early latent:
    - Single dose IM PCN
  - Late Latent or tertiary:
    - IM PCN weekly x 3 doses
  - Neurosyphilis:
    - IV PCN q4hrs for 10-14 days
- Using oral steroids without PCN may lead to exacerbation of the disease!

Review

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
<th>Uveitis Present?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Chancer</td>
<td>No</td>
</tr>
<tr>
<td>Secondary</td>
<td>Rash, Lymphadenopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Latent</td>
<td>No evidence of systemic disease</td>
<td>Yes, most common</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Cardiovascular syphilis, neurosyphilis, Benign tertiary syphilis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Foster CS. Diagnosis and treatment of uveitis

Infectious Uveitis

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Tuberculosis

- Granulomatous infection caused by Mycobacterium tuberculosis
- Primarily affect the lung, but may affect other systems (eye).
  - The bacterium likes highly oxygenated structures!

Tuberculosis incidence in the United States, 2004 and 2014

- Data from: National Tuberculosis Incidence Reporting System
- 2004 and 2014 data are from the National Tuberculosis Incidence Reporting System
- Data for 2004 is from the national Tuberculosis Incidence Reporting System and reflects the number of cases reported to the national Tuberculosis Incidence Reporting System in 2004
- Data for 2014 is from the national Tuberculosis Incidence Reporting System and reflects the number of cases reported to the national Tuberculosis Incidence Reporting System in 2014

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Ocular Involvement

- May be due to active infection or immunologic reaction to the organism
  - Scleritis
  - Phlyctenulosis
  - Interstitial keratitis
  - granulomatous uveitis (anterior and/or posterior)

Making the Dx of Tuberculosis

- Labs:
  - PPD (Purified Protein Derivative) skin test
    - Positive indicates exposure
    - Does not tell you if there is active infection
  - Interferon gamma/QuantiFerron
    - Used for those who have previously test +PPD
  - Chest x-ray
  - Bacterial culture or PCR
- Referral:
  - Internal medicine and/or infectious disease

Treating TB

- Systemic treatment
  - Initial 2-month combination course:
    - Isoniazide (INH), rifampin, and pyrazinamide daily.
    - Ethambutol is added in more resistant TB.
  - Continuation phase for an additional 4-7 months with isoniazide and rifampin
  - For latent TB, 6-9 mos of isoniazide
- Ocular treatment:
  - Steroids ideally post-systemic treatment or in conjunction with systemic therapy

The Natural History of TB Infection

- Non-Infection (70-90%)
- Infection (10-30%)
  - Dormant TB (90%) well
  - never develop TB
  - NOT infectious
  - 5% develop TB within 2 years
  - 5% develop TB many years later
  - Untreated
  - Cured

50% die within 2 years
86% of TB cases in 2014 had known HIV status at TB diagnosis.

All TB patients should have counseling and testing for HIV infection.

### Lyme Disease

- Bacterial infection caused by the *Borrelia burgdorferi* spirochete and spread via tick bites.
- Animal reservoirs: deer, horses, cows, rodents, birds, cats, dogs.
- 8.2/100,000
- Men > females
- 2 age groups:
  - 5-14yo
  - 25-50yo
- Peak time for infection: May-August
- In most cases, the tick must be attached for 36 to 48 hours or more before the Lyme disease bacterium can be transmitted.

### CDC by State

- In 2014, 15 states reported the most confirmed Lyme disease cases.
- Lyme disease is the most commonly reported vector-borne illness in the United States. It is spread by a bite from an infected tick.
- Lyme disease occurs primarily in the northeastern and upper Midwest regions of the United States.
3 Stages of Lyme Disease

- **Stage 1:**
  - Macular rash (*erythema migrans*) at the site of the tick bite.
  - Within 2-28 days in 60-80%
  - Rash may take "Bull’s Eye" pattern
  - Symptoms:
    - Fever, malaise, fatigue, myalgias, arthralgias

- **Stage 2:**
  - Occurs weeks-months following exposure where the spirochete spreads to the skin, CNS, joints, heart, and eyes.
  - Neurological involvement in 30-40% (meningitis, encephalitis, Bell’s Palsy)
  - Ocular include anterior, posterior, intermediate and pan uveitis
  - 25% of new onset Bell’s is from Lyme
• Stage 3 or persistent disease
  – Occurs 5 or more months after the infection
  – Multiple cranial nerve involvement (II, III, IV, V, VI, VII).
  – Keratitis is most common ocular finding in stage 3 followed by episcleritis
**Infectious Uveitis**

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**Most Common Infectious Underlying Etiology for AU**

- **Viral Etiologies**
  - HSV & VZV = up to 10%
  - CMV
    - HIV negative: 22.8% of AU associated with raised IOP*
  - Rubella
    - Fuch’s Heterochromia Iridocyclitis


**Clinical Features of Viral AU?**

- May vary depending on the Virus
- 50-90% of all types of viral AU:
  - Elevated IOP
  - Iris atrophy
  - KP
  - Unilateral

**HSV and VZV Clinical Features**

- **Corneal scars**
- **Corneal hypo-aesthesia**
- Sectoral iris atrophy
- Elevated IOP
- **KP**
  - Can be granulomatous, but usually smaller KP (non-granulomatous)
  - located centrally or in Ait’s Triangle
  - Medium to fine KP have been seen
- Often confused with Posner–Schlossman syndrome (PSG)

**Comparison of Herpetic Uveitis**

**HSV**
- Location:
  - 61% anterior with keratitis
  - 20% without keratitis
- **Type**:
  - Non Granulomatous 80%
  - Granulomatous 20%
- **Course**:
  - Acute: 11%
  - Chronic: 18%
  - Recurrent: 71%
- **Iris Atrophy**: 41%
- **Unilateral vs. Bilateral**: 82:18

**VZV**
- Location:
  - 58% anterior with keratitis
  - 17% without keratitis
- **Type**:
  - Non Granulomatous: 96%
  - Granulomatous: 4%
- **Course**:
  - Acute: 20%
  - Chronic: 42%
  - Recurrent: 38%
  - **Iris Atrophy**: 25%
  - **Unilateral**: 100%
  - **Past h/o zoster**

**Treatment of HSV Uveitis**

- **Topical Steroids**
  - ie: 1% prednisolone acetate ophthalmic suspension QID
- **Concurrent anti-viral!!**
  - Viroptic® (1% trifluridine ophthalmic solution) QID
  - Zirgan® (ganciclovir ophthalmic gel) 0.15% QID
  - Oral anti-viral (preferred)******
    - Valacyclovir 500mg BID
    - Acyclovir 400-800mg 5x/day
    - Less ocular toxicity with oral antivirals
    - contraindications (pregnancy).
- **Cycloplegic agents**
- **Long-term/Chronic oral antivirals to reduce recurrence rates.**
  - Year or more of tx
HEDS Study

• HEDS #3
  – Role of oral Acyclovir in epithelial HSV
    • Oral Acyclovir showed no value in short term
• HEDS #4
  – Role of oral Acyclovir in HSV iridocyclitis
    • Orals were of value, but study had only 50 pts

Subgroup HEDS Study: The Role of Oral Acyclovir

• 45% decrease in recurrence in ALL forms of HSV (epithelial, stroma, iridocyclitis)
• Effect was best demonstrated in patients with multiple recurrences
• No decrease in incidence of changing to stromal HSV
• No effect acutely but decreased recurrence

Treatment of zoster (HZV/VZV) Uveitis

• Anti-viral therapy
  – valacyclovir (Valtrex)
  – Acyclovir
• Steroids helpful, but relapses high if not treated concurrently with anti-virals
• Control IOP
  – up to 90% have high IOP
  – How to lower IOP?

Anti-Viral Dosing?

• HEDS* interpretation for active ocular disease:
  – *acyclovir, 400 mg five times per day
  – valacyclovir, 1000 mg twice per day
  – famciclovir 250 mg three times per day.
• Maintenance/prophylaxis to reduce recurrence:
  – acyclovir, 400 mg twice per day
  – valacyclovir, 500 mg daily.

Treatment of zoster (HZV/VZV) Uveitis

• Treat Inflammation
• Treat with Antivirals
• Control IOP
  – up to 90% have high IOP
  – How to lower IOP?
    • Can I use a PGA?

Will PGA Re-activate HSV?

• Purpose:
  – To determine the reactivation rate of HSV keratitis for pts treated with PGA
• Results:
  – the rate of HSV was 0.11%
  – Similar rate to normal population (0.15%)
  – No correlation with an increased risk from the use of PGA.


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CMV AU Features

- Patchy or diffuse iris atrophy
- No posterior Synechiae
- Posterior Segment is usually spared
  - Different clinical presentation from CMV retinitis which occurs in immunocompromised pts.
- Thought to be an underlying cause of PSS

Treatment of CMV Uveitis

- Studies comparing oral and topical ganciclovir
  - 75% of pt treated with orals responded BUT 3 out of 4 relapsed
  - 66% responded to topical ganciclovir
  - 25% of chronic recurred
- Recommendation:
  - Topical ganciclovir for suspected CMV AU in combination with topical steroids
Rubella Anterior Uveitis

- KP
  - Fine, diffuse, stellate KP
- Diffuse Iris Atrophy and/or Heterochromia
- No PAS
- PSC
- Vitritis
- Posterior Seg involvement
  - Sectorial peripheral retinal vascular leakage
  - CME
  - Disc hyperfluorescence on FA.
- AKA: Fuch’s Heterochromia Uveitis

Is it Possible to Differentiate Between Infectious and Non-Infectious KP?

- In vivo confocal microscopy
  - Classify KP based on appearance
    - Globular
    - Infiltrating
    - Smooth-rounded
    - Granulomatous
    - Stippled
    - Dendriform
    - More common in infectious uveitis
    - Sensitivity/specificity = 84% and 93%

Treatment for Rubella Uveitis

- Respond poorly to steroids.
- Primary goal is to control IOP and prevent loss of vision
  - Glaucomatous optic atrophy
  - PSC
    - CE/IOL
- CE/IOL

Recommendation

- A virus cause should be suspected in cases of **unilateral** anterior uveitis with iris atrophy and elevated IOPs
- **Judicious** use of corticosteroids if aqueous analysis (PCR) is not available.
- Concurrent anti-virals is appropriate and recommended

**Masquerades**

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<th>Neoplasmic</th>
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<tbody>
<tr>
<td>Retinitis Pigmentosa (RP)</td>
<td>CNS Lymphomas</td>
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<tr>
<td>Ocular Ischemic Syndrome</td>
<td>Hodgkin Lymphoma</td>
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<td>Chronic retinal detachment</td>
<td>Leukemia</td>
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<td>Intraocular FB</td>
<td>Uveal Melanoma</td>
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<td>Pigment dispersion syndrome (PDS)</td>
<td>Retinoblastoma</td>
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<td>Juvenile xanthogranuloma</td>
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<tr>
<td></td>
<td>Metastatic Tumors</td>
</tr>
</tbody>
</table>

**Non-Hodgkin’s Lymphoma**

There are two distinct forms of intraocular lymphoma.

1. **Primary CNS Lymphoma** (PCNSL) with Ocular involvement (PCNSLO)
   - when the ocular disease appears to be a subset of PCNSL.
   - Intraocular lymphoma can precede CNS involvement by months or years.

2. The secondary form of intraocular lymphoma arises outside the CNS and **metastasizes** to the eye.
The typical clinical profile is an elderly patient with uveitis that is refractory to treatment.
- Chronic and recurrent
- Subjective symptoms
  - painless decreased vision
  - photophobia
  - red eye
  - floaters.
- In some patients with known PCNSL, ocular disease may be discovered on routine screening.
- Because of its insidious onset and ability to simulate other conditions, delay in diagnosis is common.

What to do?
- Old patient, non-resolving anterior uveitis require further evaluation and NHL should be a differential diagnosis
- Labs to rule out other etiologies:
  - CBC with differential, serum immunoprotein electrophoresis, RPR screening, erythrocyte sedimentation rate (ESR), FTA-Ab test, toxoplasma titers, ANA test, rheumatoid factor, ACE, and cytomegalovirus titers
- Referral to Neurology and/or oncology
  - Identify lymph nodes and biopsy

Non-Penetrating Traumatic Anterior Uveitis

IDIOPATHIC AKA: UNDETERMINED
Thank You!

dopitz@ico.edu