Anterior Uveitis: An Organized Approach to Diagnosis and Management

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Description: This course will review the diagnosis and management of anterior uveitis. The common systemic etiologies will be reviewed along with salient symptoms and signs of each disease. Using case based examples, the lecturers will present how to tailor laboratory testing and imaging based on patient presentation.

I. UVEITIS INTRODUCTION
   A. Definition: inflammation of the uveal tissue (includes iris, ciliary body and choroid)
   B. Diverse collection of pathologic conditions that have similar clinically observable signs
   C. Classification
         a. copy posted in Canvas
      2. Anatomical
         • anatomic location focuses on site(s) of inflammation and not the presence of structural complications
         a. Anterior
            i. iritis
            ii. cyclitis
            iii. iridocyclitis
            iv. preferred: anterior uveitis
         b. Intermediate
            i. pars planitis
         c. Posterior
            i. chorioretinitis
            ii. retinochoroiditis
         d. Panuveitis
      3. Onset
         a. Sudden
         b. Insidious
      4. Duration
         a. Limited
         b. Persistent
5. **Course**
   a. Acute
   b. Recurrent
   c. Chronic

6. **Symmetry**
   a. Unilateral
   b. Bilateral

7. **Pathological Features**
   a. Granulomatous
   b. Non-granulomatous

D. **Epidemiology**
   1. most common form of ocular inflammation
   2. anterior uveitis accounts for 90% of all uveitis
   3. most common ages: 20-59
      i. corresponds with peak T-cell activity
      ii. specific disorders should be considered in young and elderly

E. **Pathophysiology**
   1. Exact pathophysiology is not known
   2. normally intraocular space is free of inflammatory cells because of blood-aqueous barrier (anteriorly) and blood-retinal barrier (posteriorly)
   3. inflammation results in tissue changes including vasodilation and increased vasopermeability
   4. Extravasation
      i. WBC (cells)
      ii. Protein (flare)
      iii. Larger MW proteins (fibrinogen → fibrin)
         - Acts like glue
         - keratic precipitates (KPs)
         - anterior synechia
         - posterior synechia

F. **Etiologies**
   1. Idiopathic
   2. Trauma
   3. Post-operative
   4. Associated with Ocular Disease
   5. Associated with Systemic Disease
II. Examination of the Patient with Anterior Uveitis

A. Symptoms
B. Ocular history
C. Medical history
D. Review of Systems (should include but not limited to...)
   1. recent ocular trauma
   2. back stiffness
   3. arthritis
   4. rashes
   5. shortness of breath
   6. urethral discharge or dysuria
   7. swollen lymph nodes, diarrhea
   8. blood in stools
   9. Recent insect bite
   10. STD
   11. TB exposure
   12. Other joint pain
   13. Nail pitting
   14. ETC...

E. Medication History
F. Family History
G. Viewing the Anterior Chamber
   1. Prior to instillation of all drops
   2. Room illumination - dark
   3. Slit lamp illumination – bright
   4. Small parallelepiped beam (SUN 1 x 1 mm)
   5. Count the cells per field
   6. Red free can block RBC

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<th>Cells in Field</th>
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<tr>
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Field Size = 1 x 1 mm beam. Adapted from SUN Working Group

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<tr>
<th>Grade</th>
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<tr>
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<td>Optically empty (compare bilaterally)</td>
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<tr>
<td>1+</td>
<td>Faint haze</td>
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<tr>
<td>2+</td>
<td>Moderate (iris and lens detail clear)</td>
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<tr>
<td>3+</td>
<td>Marked (iris and lens details hazy)</td>
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<tr>
<td>4+</td>
<td>Intense (fibrin or plastic aqueous)</td>
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Adapted from SUN Working Group
H. Problem Focused Examination

1. External Examination
2. Slit Lamp Examination
   a. Conjunctiva
      • Exceptions to circumlimbal flush
        - Juvenile Idiopathic Arthritis (JIA)
        - Fuchs' Heterochromic Iridocyclitis
      • Examine bulbar and palpebral conjunctiva for granulomas which can occur in sarcoidosis or tuberculosis
   b. Cornea
      • Test corneal sensitivity to rule out corneal hypoesthesia of herpetic keratouveitis
      • Look for evidence of current herpetic keratitis or dermatitis
      • Band Keratopathy
   c. Anterior Chamber
      • Grade cells and flare
   d. Iris
      • Nodules associated with sarcoidosis, TB, syphilis, MS, VKH, Fuchs' heterochromic iridocyclitis
      - Koeppe nodules; Busacca nodules
   e. Lens
      • Inspect phakic patients for signs of trauma: Vossius ring, rosette cataracts, etc.
      • Inspect pseudophakic patients for residual lens material, perhaps producing lens induced uveitis
   f. Vitreous
      • “Spillover” of inflammatory cells from the anterior chamber to the anterior vitreous is possible, as well as vice versa, but more commonly the former

4. Tonometry
5. Gonioscopy
6. Dilated Fundus Examination
   a. A careful Dilated Fundus Exam of the peripheral retina and posterior pole to rule out chorioretinal lesions, vasculitis or other retinal manifestations of systemic disease is a must!
III. Treatment of Anterior Uveitis

- limited clinical trials

A. Goals of Treatment
   1. preserve vision
   2. relieve ocular pain
   3. reduce ocular inflammation
   4. prevent sequelae

B. Pharmaceutical Agents Utilized
   1. topical corticosteroids
   2. cycloplegics (and mydriatics)
   3. oral corticosteroids
   4. periocular steroids
   5. immunosuppressive agents

C. Cycloplegics and Mydriatics
   1. Effects:
      a. immobilize inflamed iris
      b. prevent posterior synechia
      c. stabilize the blood-aqueous barrier

D. Topical Corticosteroids
   1. Better to overtreat than undertreat early on
   2. Which steroid?
   3. Dosing of steroid
   4. Use of ointment?
   5. Steroid taper
   6. Managing chronic cases
   7. Managing OSE
      a. Iatrogenic OHT
         i. primarily a complication of topical therapy
         ii. interference with phagocytosis in Schlemm's canal
         iii. increased accumulation of GAGs in TM
      b. ocular hypotensive medications

E. Periocular Corticosteroids
   1. more frequently utilized for intermediate uveitis (may also be used for posterior uveitis)
   2. Triamcinolone acetonide (Kenalog®; 10 or 40 mg/mL) or Methylprednisolone acetate
F. **Oral Corticosteroids**
1. can be used for recalcitrant anterior uveitis
2. Prednisone  
   a. 1-2 mg/kg (60-120 mg/day)  
   b. taper quickly  
3. Methylprednisolone  
   a. Medrol dosepak  
4. recommend H₂ receptor antagonist  
   a. cimetidine (Tagamet™) 200 mg bid  
   b. ranitidine (Zantac™) 150 mg bid

G. **Immunosuppressive Agents**
1. new agents for uveitis

H. **Overall Management**
1. initial follow-up is 1-7 days  
2. cycloplegics may be stopped more abruptly than corticosteroids  
   a. usually discontinue once flare is gone  
3. topical steroids are continued until cells are minimal (grade 0.5+) or absent  
4. tapering depends on factors such as: potency of steroid, initial severity of the uveitis and its clinical response to treatment  
5. taper may involve gradual reduction of steroids over 1-2 weeks (or longer)  
6. evaluate patient during taper and several weeks after discontinuation for signs of rebound inflammation  
7. make sure to check IOP  
8. what is the etiology?  
9. patient education

IV. **Common Etiologies of Anterior Uveitis**
A. **Acute, Nongranulomatous Anterior Uveitis**
1. idiopathic (most common)  
2. HLA-B27  
   a. Ankylosing spondylitis  
   b. Reactive arthritis  
   c. Inflammatory bowel disease  
      i. Crohn's disease  
   d. Psoriatic arthritis  
3. Behçet’s disease  
4. Rheumatoid arthritis
5. Trauma
   a. rule out other complications
   b. topical cycloplegic agent
   c. ± topical steroid
6. Postoperative
7. Infections
   a. HZ, HS, CMV
      i. HZ and HS usually secondary to keratitis but may present without corneal involvement
      ii. HSV – usually with stromal or disciform keratitis
   b. Postoperative endophthalmitis
   c. Lyme disease
   d. Syphilis
8. Lens-induced uveitis
9. UGH (uveitis-glaucoma-hyphema)

B. Chronic, Nongranulomatous Anterior Uveitis
   1. Juvenile rheumatoid arthritis (JIA)
   2. Fuchs’ heterochromic iridocyclitis
   3. Autoimmune disease

C. Granulomatous - unilateral or bilateral (rarely if ever idiopathic)
   1. Sarcoidosis
   2. Syphilis
   3. TB

V. LABORATORY TESTING IN ANTERIOR UVEITIS

A. OVERVIEW

B. CLIA (Clinical Laboratory Improvement Act)
   1. regulates all lab tests performed on humans in US
   2. www.cms.hhs.gov/clia
   3. Certificate of Waiver
   4. Approximately 80 tests
   5. must meet criteria:
      a. enroll in CLIA program
      b. pay fee biennially ($150 for waived)
      c. follow manufacturers’ test instructions
      d. “Educational” Visits
         i. 2%/year
VI. SPECIFIC TESTS

A. Angiotensin Converting Enzyme (ACE)
   1. ACE is produced by a variety of cells including granulomatous cells
      a. enzyme found mainly in lung epithelial cells
   2. reflects total amount of granulomatous tissue in the body
   3. best for patients >20 YO
   4. helps confirm diagnosis of sarcoidosis
      a. elevated in 60% of cases
   5. 12 hour fast before test

B. Antinuclear Antibody (ANA)
   1. antibodies that the body produces against its own DNA and nuclear material – causes tissue damage
   2. screening test for SLE (95%)
   3. sensitive but not specific
   4. non-specific test
      a. rheumatoid arthritis (41%)
      b. scleroderma (60-90%)
      c. Sjögren syndrome (48%)
      d. JIA WITH uveitis
   5. look at staining patterns
      a. homogenous (SLE)
      b. speckled (SLE, Sjögren syndrome, scleroderma, etc.)
      c. peripheral or rim (SLE)
      d. nucleolar (scleroderma, Sjögren syndrome)
   6. normal: nonreactive; titer <1:20
      a. titers - how many times dilution must occur to remove antibodies
   7. results in 4-5 days

C. Complete Blood Count (CBC) with differential
   1. useful in uveitis to rule out infectious etiology (and masquerade etiology)
   2. RBC cells
      a. additional info (mean cell volume, etc.)
   3. hemoglobin
4. morphology
5. hematocrit
6. platelets
7. WBC
   a. total count
   b. differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils)

D. **Erythrocyte sedimentation rate (ESR)**
   1. nonspecific test of inflammation
   2. red blood cells tend to fall to bottom of a tube of well-mixed venous blood
   3. rate at which RBCs fall is ESR
   4. reported in mm/hr
   5. \( M = \frac{\text{age}}{2} \)
   6. \( F = \frac{(\text{age} + 10)}{2} \)
   7. usually > 60 m/hr in GCA
   8. elevated during pregnancy (up to 70 mm/hr)
   9. lacks sensitivity and specificity for disease processes

E. **C-reactive protein (CRP)**
   1. abnormal serum glycoprotein produced by liver during acute inflammation
   2. disappears rapidly once inflammation subsides
   3. signifies presence of current inflammatory process
   4. 4 hour fast from food/fluids
   5. alternative to ESR
      a. more informative
      b. ESR high in most elderly
      c. no cross interference
   6. normal: no CRP (qualitative)

F. **HLA-B27**
   1. Human leukocyte antigen B-27
      a. protein found on surface of WBC
      b. HLAs used to differentiate self cells and non-self cells (immune function)
      c. different classes of HLAs have different functions
      d. HLA-B27 present in 1.4-8% of general population
         i. but is present in as many as 50-60% of patients with acute anterior uveitis
e. seronegative spondyloarthropathies
   i. by definition these patients do NOT have a positive rheumatoid factor but often mimic rheumatoid arthritis
   ii. Inflammatory joint disease of the vertebral column
   iii. Examples: Ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, psoriatic arthritis
f. NORMAL: negative

G. Rheumatoid Factor (RF)
1. immunoglobulin that appears in serum and synovial fluid several months after onset of rheumatoid arthritis and is present up to several years after therapy
2. Positive titers in numerous collagen vascular diseases
3. (+) in 70-80% of patients with rheumatoid arthritis
4. Also (+) with:
   a. SLE
   b. Sjögren’s
   c. TB
   d. sarcoid
   e. viral infection
5. Negative finding most useful
6. Normal: titer < 1:20
7. Titers 1:40-1:60 are diagnostic for rheumatoid arthritis
8. Titers >1:60 are indicative of advanced rheumatoid arthritis

H. perinuclear-Antineutrophil Cytoplasmic Antibody (p-ANCA)
1. ANCA are autoimmune antibodies directed against the lysosomal enzymes in neutrophil granules.
2. p-ANCA antibody pattern is similar to that of ANA
3. p-ANCA is elevated in Crohn disease
4. c-ANCA (classical) – only test available for the diagnosis of vasculitis
5. Normal: negative; titer < 1:40

I. Purified Protein Derivative (PPD)
1. TB skin test
2. inject under skin
3. check in 48-72 hours
4. normal: zone of redness and induration < 5mm
   a. chest X-Ray indicated for all positive tests
5. Positive for active and inactive TB
J. **Syphilis Testing**
1. RPR (rapid plasma reagin) test
2. VDRL (venereal disease research laboratory) test
   a. more sensitive than RPR for primary syphilis
3. FTA-ABS (fluorescent treponemal antibody absorption) test
4. MHA-TP (microhemagglutination treponemal pallidum) test

K. **Radiologic Studies**
1. Chest X-Ray
2. Sacroiliac joint
3. other affected joints

VII. **Disease Descriptions**

A. **Rheumatoid Arthritis**
1. autoimmune disorder
2. chronic systemic inflammatory disease
3. synovial joints affected
4. W>M
5. 40-50
6. **Laboratory Testing**
   a. X-Rays of hands and feet
   b. Rheumatoid Factor (RF)
   c. Anti-cyclic citrullinated peptide antibody (anti-CCP)
      i. powerful biomarker to allow early diagnosis

B. **Juvenile Idiopathic Arthritis (JIA)**
1. most common form of arthritis <16 YO
2. may be transient and self-limiting or chronic
3. idiopathic inflammatory arthritis
4. 3 subgroups
   a. **Oligoarticular JIA (Pauciarticular) – 50% of cases**
      i. four or less joints are involved during first 6 months
      iii. 30% of patients develop uveitis
   b. **Polyarticular JIA – 20% of cases**
      i. the disease affects 5 or more joints – smaller joints often affected
      ii. Uveitis may occur
   c. **Systemic JIA- 30% of cases**
      i. Uveitis EXTREMELY rare
5. Ocular inflammation may precede or follow the arthritis
6. The non-granulomatous anterior uveitis often results in posterior synechia, cataract formation or characteristic band keratopathy
7. **Laboratory Testing**
   a. X-rays of affected joints
   b. Rheumatoid factor
   c. Anti-nuclear antibody (ANA)

C. **Sarcoidosis**
   1. unknown etiology
   2. multisystem granulomatous inflammatory disease
   3. peak incident is 20-30; second peak >50
   4. W>M
   5. In US; more common in AA
   6. also more common among the Scandinavian population
   7. 50% have ocular complications
   8. **Laboratory Testing**
      a. Chest X-Ray
      b. Serum Angiotensin Converting Enzyme (ACE)
      c. Biopsy of conjunctival granulomas
      d. serum lysozyme
      e. serum calcium
      f. gallium scan
      a. Chest X-Ray
      b. Purified protein derivative (PPD)

VII. **Differential Diagnosis of Anterior Uveitis**
A. Posner-Schlossman Syndrome (Glaucomatocyclitic Crisis)
B. Masquerade Syndromes
   1. Retinal detachment
   2. Malignant melanoma
   3. Leukemia, lymphoma
   4. Intraocular foreign body
   5. Ocular ischemic syndrome
   6. etc.

VIII. **Final Words on Uveitis**
A. First episode of mild, unilateral nongranulomatous anterior uveitis – usually a “freebie”
B. Era of shotgun approach to laboratory testing has passed
C. Order appropriate tests based on clinical picture
D. Make appropriate referrals as indicated, e.g. rheumatology or internal medicine etc.