Ocular Manifestations in Autoimmune Diseases

Blair B Lonsberry, MS, OD, MEd., FAAO
Diplomate, American Board of Optometry
Clinic Director and Professor of Optometry
Pacific University College of Optometry
blonsberry@pacificu.edu
Disclosures and Special Request

Paid consultant for:

- Alcon Pharmaceuticals, Bausch and Lomb, Carl Zeiss Meditec, Sucampo, Valeant

Special Request:

Interactive remotes don’t work on your TV, so please don’t take them home! 😊

Commitment to change:

- write down three things that you “learned” from this presentation that you can incorporate into your practice to improve patient care
- revisit these points a month from now, again in 3 months and 6 months and see if you have adopted them
- make a commitment to change how you care for patients!
Autoimmune Diseases

• Group of acquired diseases in which genetic factors appear to play a role
• They have in common widespread immunologic and inflammatory alterations of connective tissue
• The illnesses share certain clinical features and differentiation between them is often difficult because of this.
• Although thought to be acquired diseases, often their causes cannot be determined.
Agenda

- Rheumatoid Arthritis
- Lupus
- Sjogrens
- HLA Conditions:
  - Ankylosing spondylitis
  - Psoriatic arthritis
  - Reactive arthritis
  - Enteropathic arthritis
- Juvenile Idiopathic Arthritis (JIA) formerly Juvenile Rheumatoid Arthritis (JRA)
CASE
Case History

- 49 WF presents with a complaint of blurry/fluctuating vision at distance and near
- PMHx:
  - Hypertension 15 years
  - Review of Systems:
    - Joint pain
    - Seasonal allergies
    - Ocular: dryness, redness, burning, blurriness
- POHx: no surgeries or trauma reported
- Meds: HCTZ
  - Celebrex for joint pain
Entrance Skills

• VA (corrected):
  - +1.00 – 0.50 x 180 20/25
  - +1.00 – 0.50 x 180 20/25

• All other entrance skills unremarkable

• Refraction:
  - +1.25 – 0.50 x 180 20/25
  - +1.25– 0.75 x 180 20/25

  • Patient notes vision “still not quite right” and “fluctuating”
**OD**
- Clear-Adnexa/Orbit-Clear
- Meibomian Capping-LLL-Meibomian Capping
- Conj Redundancy-1st Invasion Conj Redundancy
- 1st Injection
- White-Sclera-White
- Z+ SPK-Cornea-Z+ SPK
- (bulb, palp)
- 4sec-TBUT-5sec
- 4x4-Angle-4x4
- D/Q-AC-D/Q
- (cell/flare)
- Brown-Iris-Brown
- Clear-Lens-Clear
- (ant., post. caps, cortex, nucleus)
- Clear-Vitreous-Clear

**OS**
- Clear-Adnexa/Orbit-Clear
- Meibomian Capping-LLL-Meibomian Capping
- Conj Redundancy-1st Invasion Conj Redundancy
- 1st Injection
- White-Sclera-White
- Z+ SPK-Cornea-Z+ SPK
- (bulb, palp)
- 4sec-TBUT-5sec
- 4x4-Angle-4x4
- D/Q-AC-D/Q
- (cell/flare)
- Brown-Iris-Brown
- Clear-Lens-Clear
- (ant., post. caps, cortex, nucleus)
- Clear-Vitreous-Clear

**BP** 150/88

**Tonometry Time**
- OD 18 mmHg TAG
- OS 18 mmHg PEN

**ANESTH.**
- 1/2 Hydroxocodone

**Discussed side effects of dilation** 5 C

**Dilated:**
- M 0.5%, 1%
- N 2.5%, 10%
- C 1%
- OD OS (OU)

**Lenses:**
- 20 D
- 90 D
- 78 D

**3 Mirror Indent extended opth.**

**time:** 2:00 PM
Flat, Pink, Distinct OU

Disc
25 (size, color, NFL) +3
25 + C/D +3

VESSELS
+ SVP +
1/2 A/V 1/2
1/3 ALR 1/3

MACULA
- FLR -

PERIPHERY
<3 Holes, Teas, Detachment
360° OU

Flat, Black Lesions
W/ Distinct Borders
Do Not Disappear W/ Red Free
RHEUMATOID ARTHRITIS
Rheumatoid Arthritis

- Collagen vascular disorders:
  - most common form of inflammatory joint disease
  - lead to most common form of physical disability in the US
- Average onset between 35-50
- Familial predisposition
- 3x more females
- Predominately Caucasian

Figure 3. Joint frequently affected by rheumatoid arthritis. Less commonly affected are elbows, hips and the neck.
Rheumatoid Arthritis

- Rheumatoid Arthritis (RA) is not a benign disease.
- RA is associated with decreased life expectancy.
  - The risk of cardiovascular mortality is twice that of the general population.
- Affecting approximately 1% of the adult population, RA is associated with considerable disability.
Rheumatoid Arthritis

- RA adversely impacts an individual’s quality of life and results in increased financial burden both to the individual and society through medical costs and loss of productivity.
- It is now well recognized that there is a "window of opportunity" early in the disease process to initiate treatment which will fundamentally change the course of the disease.
Rheumatoid Arthritis
Epidemiology-Systemic

- Primary sites of inflammation are centered around musculoskeletal tissues
  - small joints with synovial linings are most commonly affected ie hands/feet early in disease
- RA joint characterized by hypertrophic, inflamed synovial tissue with fluid accumulation and adjacent soft tissue swelling
  - this is responsible for hot, swollen, tender joints that are hallmark of RA
# Other Diagnostic Criteria for RA

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Ocular</th>
<th>Pulmonary</th>
<th>Cardiac</th>
<th>Neurological</th>
<th>Hematological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules</td>
<td>Sicca</td>
<td>Pleuritis</td>
<td>Pericarditis</td>
<td>Peripheral neuropathy</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Episcleritis</td>
<td>Nodules</td>
<td>Atherosclerosis</td>
<td>Cervical myelopathy</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Interstitial lung disease</td>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Common sites for rheumatoid nodules

1. Pain source.
2. Pain messages move through peripheral nerves and up the spinal cord.
3. Your brain interprets the messages as pain, including its location, intensity and nature (burning, aching, stinging).
4. Your brain sends pain-suppressing chemicals to the pain source and triggers other responses.
**Osteoarthritis (OA) vs. RA**

- **Etiology of RA** is inflammatory which improves with activity while osteo is mechanical and worsens with activity.
- **Inflammation** secondary to mechanical insults in osteo while no previous insult required in RA.
- **Joint cartilage** is primary site of articular involvement in osteo while its the bony surfaces of the joints in RA.
Diagnosis

• Many patients have symptoms that are not exclusive to RA making diagnosis difficult
  – prodromal systemic symptoms of malaise, fever, weight loss, and morning stiffness

• Lab tests and radiographic studies are necessary for initial diagnosis and are helpful in monitoring progression
  – no one single test is confirmatory of disease
Criteria for Diagnosis of RA

RA likely if:

- Morning stiffness > 30 minutes
- Painful swelling of 3 or more joints
- Involvement of hands and feet (especially MCP and MTP joints)
- Duration of 4 or more weeks
- Differential diagnoses include: crystal arthropathy, psoriatic arthritis, lupus, reactive arthritis, spondyloarthropathies.
# Lab Testing for RA

<table>
<thead>
<tr>
<th>Tests</th>
<th>Diagnostic Value</th>
<th>Disease Activity Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR or CRP</td>
<td>Indicate only inflammatory process - Very low specificity</td>
<td>ESR elevated in many but not all active inflammation. Maybe useful in monitoring disease activity and response to treatment</td>
</tr>
<tr>
<td>RF</td>
<td>RF has a low sensitivity and specificity for RA. Seropositive RA has worse prognosis.</td>
<td>No value</td>
</tr>
<tr>
<td>ANA</td>
<td>Positive in severe RA, SLE, or other connective tissue disorders (CTD)</td>
<td>No value-do not repeat</td>
</tr>
<tr>
<td>X-rays</td>
<td>Diagnostic erosions rarely seen in disease of &lt;3 mo’s duration</td>
<td>Serial x-rays over many years may show disease progression and indicate med change</td>
</tr>
<tr>
<td>Joint aspiration</td>
<td>Indicated if infection suspected</td>
<td></td>
</tr>
</tbody>
</table>
Rheumatoid Factor (RF)

• RF is an autoantibody directed against IgG
• Most common lab testing are latex fixation and nephelometry
• RF present in 70-90% of patients with RA
  – However RF is not specific for RA
  – Occurs in a wide range of autoimmune disorders
  – Prevalence of positive RF increases with age
    • As many as 25% of persons over age of 65 may test positive
  – High titer for RF almost always reflects an underlying disease
Rheumatoid Factor (RF)

- Indication:
  - RF should be ordered when there is clinical suspicion of RA
- Interpretation
  - Positive test depends on pretest probability of the disease
    - If other clinical signs present can provide strong support for diagnosis of RA
    - Keep in mind that the combination of a positive test is not specific for RA
  - Negative test should not completely rule out possibility of RA
    - From 10-30% of patients with long-standing disease are seronegative
    - The sensitivity of the test is lowest when the diagnosis is most likely to be in doubt
Antibodies to Cyclic Citrullinated Peptides (anti-CCP)

• Proteins that contain citrulline are the target of an AB response that is highly specific for RA
• Anti-CCP detected using ELISA
• Associated conditions:
  – Appears to be quite specific for RA
    • Specificity as high as 97%
  – Sensitivity in the range of 70-80% for established RA and 50% for early-onset
  – Has superior specificity and comparable sensitivity for diagnosis of RA as compared to RF
Antibodies to Cyclic Citrullinated Peptides (anti-CCP)

Indication:
- Should be ordered when there is a clinical suspicion of RA

Interpretation:
- Presence provides strong support for the diagnosis of RA
- In patients with early onset, undifferentiated, inflammatory arthritis positive results are a strong predictor of progression to RA and the development of joint erosion
- Negative test does not exclude possibility of RA particularly at the time of initial presentation (apprx 50% of patients lack detectable antibodies)
Diagnosis

- Joint x-ray and radionucleotide evaluation of suspected inflamed joints are indicated.
Rheumatoid Arthritis: Treatment

- Treatment must be started early to maximize the benefits of medications and prevent joint damage.
- The use of traditional medications in combination and the new biologic therapies has revolutionized the paradigm of RA treatment in recent years.
- The approach to care of patients with RA should be considered as falling into two groups.
  - Early RA (ERA) is defined as patients with symptoms of less than 3 months duration.
  - Patients with established disease who have symptoms due to inflammation and/or joint damage.
Treatment and Management-Systemic

- The treatment approach varies depending on whether the symptoms arise from inflammation or joint damage making the differentiation vital.
- There is no curative treatment for RA
  - treatment is to minimize inflammation
  - minimize damage and
  - maximize patient functioning.
- Pharmaceutical agents inhibit inflammatory responses
  - have traditionally been used in a stepwise approach from weakest to strongest.
Treatment and Management-Systemic

• Current Tx regimens utilize a step-down approach with initiation of one or more DMARD’s at time of diagnosis.
• RA most destructive early in disease
• “Easier” and more effective if Tx initiated early.
• DMARD-disease modifying antirheumatic drug
  – these drugs not only reduce inflammation but also change the immune response in a long-term and more dramatically than NSAID’s
  – give chance of permanent remission
Treatment and Management: Aspirin and NSAID’s

- block infl’n by inhibition of prostaglandin release in response to cell trauma
- arachadonic acid converted by COX (1&2) enzymes into inflammatory mediators including:
  - Thromboxanes
  - Prostaglandins
  - Leukotrienes
Treatment and Management: Aspirin and NSAID’s

- aspirin and NSAID’s inhibit both and used in initial Tx for pain but don’t inhibit progression of disease
- newer selective COX 2 inhibitors avoid GI upset
  - COX 1 needed for GI protective PG’s but have CV toxicity
Treatment and Management: Steroids

- steroids interfere with all facets of the inflammatory process and effectively shut it down
- rapidly bring down joint infl’n and increase physical function and reduce progression of joint damage
Treatment and Management: Steroids

- have serious SE’s such as
  - osteoporosis, HTN,
  - peptic ulcers,
  - vascular disease, cataracts,
  - glaucoma,
  - mood changes, etc
- usually used in short-term pulse dosages (e.g. 7.5 mg/day in combination with DMARD to reduce joint damage in early disease Tx).
Treatment and Management: Antimalarials

- hydroxychloroquine more common and less toxic than more effective chloroquine
- usual dose is 200-400 mg/d @night with onset of action after a period of 2-4 months
- has mild DMARD effect, does not slow radiographic progression and has relatively slow onset of action, useful with other DMARD’s
Treatment and Management: Antimalarial Ocular Complications

• Have affinity for pigmented structures such as iris, choroid and RPE
• Toxic affect on the RPE and photoreceptors leading to rod and cone loss.
• Have slow excretion rate out of body with toxicity and functional loss continuing to occur despite drug discontinuation.
Question

Which of the following depicts a retina undergoing hydroxychloroquine toxicity?

ARMD

Macular Hole

OHS

Bull’s Eye Maculopathy
Treatment and Management: Antimalarial Ocular Complications

• Toxicity can lead to whorl keratopathy, “bulls eye” maculopathy, retinal vessel attenuation, and optic disc pallor.

• Early stages of maculopathy are seen as mild stippling or mottling and reversible loss of foveal light reflex

• “Classic” maculopathy is in form of a “bulls eye” and is seen in later stages of toxicity
  – this is an irreversible damage to the retina despite discontinuation of medication
Treatment and Management: Antimalarials

Bulls Eye Maculopathy

Whorl Keratopathy
Fabry Disease

• alpha-galactosidase-A deficiency.
  – insufficient breakdown of lipids, which build up to harmful levels in the eyes, kidneys, autonomic nervous system, and cardiovascular system.
• Fabry disease is one of several lipid storage disorders and the only X-linked lipid storage disease.
• Lipid storage may lead to impaired arterial circulation and increased risk of heart attack or stroke.
  – The heart may also become enlarged and the kidneys may become progressively involved.
• Other signs include decreased sweating, fever, and gastrointestinal difficulties.
Revised Recommendations on Screening for Retinopathy

• 2002 recommendations for screening were published by Ophthalmology

• Revised recommendations on screening published in Ophthalmology 2011;118:415-42
  – Significant changes in light of new data on the prevalence of retinal toxicity and sensitivity of new diagnostic techniques
  – Risk of toxicity after years of use is higher than previously believed
    • Risk of toxicity approaches 1% for patients who exceed 5 years of exposure
Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- Screening Tests: **Newer objective tests, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available.** When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for evaluation by objective testing. Because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull’s-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage.
Revised Recommendations on Screening for Retinopathy

• Amsler grid testing removed as an acceptable screening technique
  – NOT equivalent to threshold VF testing
• Strongly advised that 10-2 VF screening be supplemented with sensitive objective tests such as:
  – Multifocal ERG
  – Spectral domain OCT
  – Fundus autofluorescence
Revised Recommendations on Screening for Retinopathy

• Parafoveal loss of visual sensitivity may appear before changes are seen on fundus evaluation
  • Many instances where retinopathy was unrecognized for years as field changes were dismissed as “non-specific” until the damage was severe
  • 10-2 VF should always be repeated promptly when central or parafoveal changes are observed to determine if they are repeatable
  • Advanced toxicity shows well-developed paracentral scotoma
Paracentral Scotomas
Revised Recommendations on Screening for Retinopathy

• SD-OCT can show localized thinning of the parafoveal retinal layers confirming toxicity
  – not appreciable with time-domain OCT
  – changes maybe visible prior to VF defects
• Fundus autofluorescence may reveal subtle RPE defects with reduced autoFL or show areas of early photoreceptor damage
• MF-ERG can objectively document localized paracentral ERG depression in early retinopathy
Normal Retina: VF/OCT/ERG

PIL=PR Integrity Line
Mild Maculopathy

Thinned Outer Nuclear Layer

PIL

Paracentral Scotomas

Normal Foveal Peak

Bull’s Eye Maculopathy

Revised Recommendations on Screening for Retinopathy

<table>
<thead>
<tr>
<th>Factors Increasing Risk of Retinopathy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use</td>
<td>&gt; 5 years</td>
</tr>
<tr>
<td>Cumulative Dose</td>
<td>&gt; 1000 g (total)</td>
</tr>
<tr>
<td>Daily Dose</td>
<td>&gt; 400 mg/day</td>
</tr>
<tr>
<td>Age</td>
<td>Elderly</td>
</tr>
<tr>
<td>Systemic Disease</td>
<td>Kidney or liver dysfunction</td>
</tr>
<tr>
<td>Ocular Disease</td>
<td>Retinal disease or maculopathy</td>
</tr>
</tbody>
</table>
Treatment and Management: Methotrexate

- now considered as part of mainstay treatment
- antimetabolite used in cancer therapy that inhibits DNA synthesis (thought to cause suppression of lymphocyte proliferation)
- low dose in RA (7.5-25mg) once weekly orally or injection with onset of action 6-8 weeks
Treatment and Management: Methotrexate

- toxicity not uncommon but adverse events tend to be minor and can be managed by cessation of drug.
- Supplement of folic acid prevents common SE of oral ulceration and nausea.
- serious complications of lung disease and fibrosis with incidence of 3-15% and fatality of 17%.
Treatment and Management: Biological Therapies-TNF Inhibitor

- High concentration of TNF-alpha in synovial fluid in RA and increased in areas of bone erosions
- TNF-alpha released in cell damage and binds to receptors that increase the inflammatory process and cell death
Treatment and Management: Biological Therapies-TNF Inhibitor

- inhibitors bind TNF before it can be bound to the receptor (infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira]) and newest golimumab (Simponi)
- quicker onset of action (several weeks)
- new studies indicate use as first line therapy, potentially combined with methotrexate
Treatment and Management: Biological Therapies-TNF Inhibitor

- Remicade: 3 mg/k as IV infusion followed by similar doses at 2 and 6 weeks and then every 8 weeks after
- Enbrel and Humira are SC injections every 2 weeks
- Newest is Simponi which is once a month injection
- Adverse affects include increased risk of opportunistic infections (TB most common), malignancies (lymphoma) and neurological disease.
- common SE’s include nausea and vomiting
Ocular Manifestations: Dry Eye

• Most common ocular complication is dry eye
• >95% of patients suffer from dry eye signs and symptoms
• Compromised cornea can lead to bacterial keratitis
Differential Diagnosis of Dry Eye

DRY EYE

Deficient Aqueous Tear Production
  - Sjögren syndrome
  - Non-Sjögren Syndrome

Increased Evaporative Loss
  - Blepharitis/Meibomian Gland Dysfunction
  - Exposure
  - Other factors
    1. Contact lenses
    2. Blink abnormality
    3. Environmental
Aqueous Deficient Dry Eye Pathophysiology

Production of cytokines

Interrupted nerve impulses

Chronic irritation of ocular surface

Cytokine secretion into tears

Disruption of normal tearing control

Cytokines disrupt nerve circuit
# Treatment/Management

<table>
<thead>
<tr>
<th>DTS Severity</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No treatment</td>
</tr>
<tr>
<td></td>
<td>Preserved tears</td>
</tr>
<tr>
<td></td>
<td>Environmental management</td>
</tr>
<tr>
<td></td>
<td>Allergy drops</td>
</tr>
<tr>
<td></td>
<td>Use of hypoallergenic products</td>
</tr>
<tr>
<td></td>
<td>Water intake</td>
</tr>
<tr>
<td></td>
<td>Psychological support</td>
</tr>
<tr>
<td></td>
<td>Avoidance of drugs contributing to dry eye</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Unpreserved tears</td>
</tr>
<tr>
<td></td>
<td>Gels</td>
</tr>
<tr>
<td></td>
<td>Ointments</td>
</tr>
<tr>
<td></td>
<td>Nutrient support (fatty acids)</td>
</tr>
<tr>
<td></td>
<td>Secretagogues</td>
</tr>
<tr>
<td></td>
<td>Topical steroids</td>
</tr>
<tr>
<td></td>
<td>Topical cyclosporine</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Punctual plugs</td>
</tr>
<tr>
<td>Tier 4</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Systemic anti-inflammatory therapy</td>
</tr>
<tr>
<td></td>
<td>Oral cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Moisture goggle</td>
</tr>
<tr>
<td></td>
<td>Punctal cautery</td>
</tr>
<tr>
<td></td>
<td>Acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>Contact lenses</td>
</tr>
</tbody>
</table>
Ocular Manifestations-Episcleritis

- Episcleritis can be presenting sign for RA
- Unilateral (bilateral possible but rarely simultaneously)
- Recurrent episodes of episcleritis usually manifest prior to active periods of arthritis and a better indicator than dry eye
- Episcleritis will recur despite systemic treatment
Treatment and Management: Episcleritis

- Treatment of episcleritis is dependent upon severity and chronicity.
- Palliative care maybe considered for mild cases (ocular lubrication).
- Utilization of vasoconstrictors, NSAIDs and steroid (Pred mild, Lotemax) use for more severe or chronic cases.
Ocular Manifestations-Scleritis

- Diffuse and nodular forms
- Necrotizing (with/without inflammation) less frequent
  - Have the most serious systemic implications
  - Scleromalacia perforans
Treatment and Management: Scleritis

• Scleritis treatment depends on both the type and severity.
• Aggressive treatment is necessary in order to prevent structural damage.
• Oral NSAIDs are mainstay treatment (indomethacin 50 mg BID to TID po)
  – maybe combined with oral steroids (Prednisone 60-100 mg po qd).
  – Topical steroids are ineffective in treatment of the scleritis but may be used to manage any associated uveitis.
  – Steroid use is contraindicated when scleral thinning is present because of potential for perforation.
Treatment and Management: Scleritis

• If necrotizing present patient needs to receive aggressive medical therapy by rheumatologist
  – patients have better prognosis when immunosuppressive therapy is instituted
Case

- 30 BF presents with eye pain in both eyes for the past several days
  - Severe pain (8/10)
  - Never had eye exam before

- PMHx:
  - Has chronic bronchitis
  - Rash on legs
  - Has recently lost weight and has a fever
  - Taking aspirin for pain
Ocular Health Assessment

- VA: 20/30 OD, OS
- PERRL
- FTFC
- EOM”s: FROM with eye pain in all quadrants
- SLE: 3+ injection, 3+ cells and trace flare, deposits on endo (see photo)
- IOP: 18, 18 mmHg
- DFE: sheathing of posterior pole vasculature, vitreal cells, and white fluffy deposits at ora.
Ocular Manifestations-Uveitis

• Non-granulomatous uveitis is sometimes found
• Signs/symptoms include:
  – pain,
  – photophobia,
  – blurred vision,
  – ciliary flush,
  – cells/flare,
  – rarely posterior involvement
Helpful Mnemonic

- Mnemonic for acute forms of non-granulomatous uveitis: BLAIR G
  - B: Behcet’s disease
  - L: Lyme disease
  - A: Ankylosing spondilitis
  - I: Irritable bowel syndrome (Crohn’s)
  - R: Reactive arthritis
  - G: Glaucomatocyclitic crisis
Ciliary Flush, Cells, Flare
Uveitis: Treatment

– “Classical treatment”:
  • Pred forte: every 1-2 hours, ensure taper
    – Pred forte: prednisolone acetate formulation which allows penetration through cornea to anterior chamber

– Newer treatment option:
  • Durezol
Treatment options

• Durezol:
  – Difluprednate
    • only difluorinated steroid
  – Steroid emulsion
  – BAK free
  – Increased “potency” so dosing needs to be less than “classical treatment” with Pred Forte
    • rough recommendation is 1/2 dosing of Pred Forte
Treatment: Cycloplegia

– Homatropine (cycloplegia):
  • BID
    – for pain,
    – prevention of synechiae, and
    – reduction of inflammation
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
Systemic Lupus Erythematosus (SLE)

- Idiopathic, multisystemic inflammation disorder characterized by hyperactivity of immune system and prominent auto-antibody production
  - against components of cell membranes and nuclear material
- Acute periods followed by periods of remission are common
  - gives disease an unpredictable course
Systemic Lupus Erythematosus (SLE)

• Definite genetic predisposition has been demonstrated
  – environmental factors also play a role especially as triggers

• Clinical course varies from mild episodic disorder to rapidly developing fatal disease
Epidemiology

- SLE is not uncommon with prevalence exceeding 1:2000 persons with 85% being female
- Disease may occur at any age though most patients are b/w ages 20-40
  - AA being affected 3x more than any other race (and more severely)
Epidemiology

• Have to ensure that condition is not secondary to a drug response (several drugs produce lupus-like syndrome)

  – Agents strongly associated include:
    • Procainamide (cardiac arrhythmias), hydralazine (high blood pressure) and isoniazid (anti-tuberculosis)
    • Others include: phenytoin, quinidine, tetracyclines and TNF inhibitors.
Diagnosis

• Based on clinical presentation and lab results

• Systemic features include
  – fever
  – anorexia
  – malaise and
  – weight loss.

• Most patients have skin lesions at some time with the characteristic “butterfly” rash (occurs apprx 50%) and often precedes disease manifestations
Diagnosis

- Joint symptoms (with/without active synovitis) occur in >90% of patients and are often the earliest manifestation.
- Other organs affected include heart, kidney, lungs, CNS.
- American Rheumatololgy Association established 11 criteria for diagnosis (8 clinical manifestations and 3 lab).
  - Minimum of 4 needed serially or simultaneously.
Lab Tests:
Antinuclear Antibodies (ANA)

• AB’s directed against nuclear material:
• Detection is via indirect immunofluorescence
  • ANA with titers ≥ 1:40 considered positive
• Associated conditions:
  – Positive tests occur in a wide variety of conditions
    • Low-titer ANA are relatively common among healthy adults
## Conditions Associated with Positive ANA

<table>
<thead>
<tr>
<th>Rheumatic Diseases</th>
<th>Organ-Specific AI Diseases</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>AI thyroid disease</td>
<td>Drug-induced lupus</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>AI hepatitis</td>
<td>Asymptomatic drug-induced ANA</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Primary biliary cirrhosis</td>
<td>Chronic infections</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>AI cholangitis</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>Polymyositis</td>
<td></td>
<td>Lymphoproliferative disorders</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td></td>
<td>Type 1 diabetes (ketoacidosis)</td>
</tr>
<tr>
<td>Discoid Lupus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lab Tests:
Antinuclear Antibodies (ANA)

• Indications:
  – Very useful initial test when there is clinical suspicion of:
    • SLE,
    • drug induced lupus
    • Mixed connective tissue disease
    • Scleroderma

• Interpretation:
  – Sensitivity of ANA for SLE is very high (>95%)
    • Negative result is very strong evidence against the diagnosis and usually precludes the need to pursue further testing
Lab Tests:
Antinuclear Antibodies (ANA)

• Interpretation:
  – Probability of an underlying AI disease increases with the titer of the ANA
  – In an unselected population:
    • Positive test has a predictive value for SLE of 30-40%
    • Negative predictive value for SLE is >99%
  – In proper clinical context a positive ANA provides support for further testing for SLE
Lab Tests: Antibodies to Double-Stranded DNA

- **ELISA is most commonly used**
- **Associated conditions:**
  - Occurs in SLE and is rare in other diseases and in healthy persons
- **Indications:**
  - Should be measured when there is clinical suspicion of SLE and the ANA is positive
- **Interpretation:**
  - Specificity for SLE is 97% and approaches 100% when titer is high
  - AB’s occur in 60-80% of patients with SLE
Lab Tests

• Decreased serum complement C1 level is 90% predictive for SLE and C4 is 75%
  – simultaneous presence of both a decreased C1 level and native DNA Ab’s has been reported to be virtually 100% predictive

• Decreased serum complement levels result from activation and consumption of complement components
Treatment and Management

• No cure for SLE (rest, reduce stress and avoid UV exposure)

• Medical management includes:
  – Salicylates and NSAIDs employed to treat arthralgias, arthritis, myalgias and fever in 20-30% of Px with mild disease
  – Antimalarials (Plaquinil) used to treat discoid lesions and joint disease
  – High dose, short-acting steroids are used in life-threatening and severely disabling cases. Prolonged maintenance at low dosages needed after.
  – Cytotoxic controversial-used when steroids ineffective
  – Exp therapy: high dose immunoglobulin injections
Ocular Manifestations

- SLE produces various ocular complications which tend to manifest in more acutely ill patients.
- Retinal vasculopathy is believed to be due to autoimmune reactions to Ab/Ag complexes deposited in the retinal/choroidal vessel walls.
- Common retinal finding include:
  - Cotton wool spots (CWS)
  - Retinal hemes
Ocular Manifestations

- Occlusions are uncommon but occur more frequently in arteries and can result in nonperfusion and hypoxia.
- Optic nerve and retinal neo may arise.
- Vitreous heme and RD may also occur.
- Optic atrophy and blindness may result in severe occlusions.
Ocular Manifestations

- SPK most common corneal change
- In patients with uncontrolled systemic disease sicca syndrome is common
- Occasional corneal manifestations may include infiltrates, ulcers and neo.
Ocular Manifestations

- Scleritis is usually diffuse and nodular and is fairly common. It may be the presenting feature of SLE.
- Non-granulomatous uveitis is sometimes found.
- Diplopia and pupillary abnormalities secondary to cranial nerve palsies also arise.
SJOGREN’S SYNDROME
Case

• 55 yr white female complains of fluctuating vision
  – Worse at near
  – Spends 8-10 hours/day on the computer

• Medical Hx:
  – Hypertension for 10 years
  – Joint pain

• Medications:
  – HCTZ for HTN
  – Celebrex for her joint pain
Exam Data

- VA (corrected): OD: 20/25, OS: 20/25
- PERRL
- EOM’s: FROM
- CVF: FTFC
- SLE:
  - TBUT 5 sec OD, OS
  - Positive NaFl staining and Lissamine green staining of conj and cornea
  - Decreased tear prism
Additional Testing/Questions

• Schirmer: < 5 mm of wetting in 5 minutes OD, OS
• RF and ANA: normal for patients age
• SS-A: 2.0 (normal < 1.0), SS-B: 1.9 (normal <1.0)
• Additional symptoms reported:
  – Patient experiences dry mouth and taking Salagen

• **Diagnosis: Sjogren’s Syndrome**
Differential Diagnosis of Dry Eye

DRY EYE

Deficient Aqueous Tear Production
- Sjögren Syndrome
- Non-Sjögren Syndrome

Increased Evaporative Loss
- Blepharitis/Meibomian Gland Dysfunction
- Exposure
- Other factors
  1. Contact lenses
  2. Blink abnormality
  3. Environmental
Signs and Symptoms of Dry Eye

**Signs:**
- Ocular Surface Damage
  - Corneal Staining (Fluorescein and/or Rose Bengal)
  - Conjunctival Staining (Lissamine Green)
- Decreased Tear Quantity
  - Schirmer Score
  - Phenol Red Thread Test
  - Tear Meniscus Height
- Decreased Tear Quality
  - Tear Break Up Time (TBUT)
  - Tear Osmolarity

**Symptoms:**
- Grittiness
- Burning
- Irritation
- Stringy discharge
- Blurring of vision
- Ocular Surface Disease Index (OSDI)
Treatment

• We initiated:
  – Omega-3 supplements (3-4 grams per day)
  – Recommended warm compresses and lid washes qhs
  – Testosterone cream 3% applied to upper lid bid

• Patient had significant improvement in symptoms with the use of the topical testosterone cream.
  – However, she was still symptomatic at the end of the day and she still had significant staining on her cornea and conjunctiva
  – Initiated FML tid for 1 month, restasis bid after 2 weeks
    • 2 months later patient reported further improvement in her symptoms
    • No conjunctival staining was noted and only slight SPK
    • Schirmer values improved to OD: 9 mm, OS: 10 mm
Transdermal Testosterone Cream

• Recent studies have suggested that androgen deficiency may be the main cause of the meibomian gland dysfunction, tear-film instability and evaporative dry eye seen in Sjogren patients.
• Transdermal testosterone promotes increased tear production and meibomian gland secretion, thereby reducing dry eye symptoms (Dr. Charles Connor).
• arGentis and Allergan have conducted trials to see if topical androgens are effective in treating dry eye.
SJOGREN’S SYNDROME: OLD/NEW CLASSIFICATION

• Old:
  – 1° Sjogrens: occurs when sicca complex manifests by itself
    • no systemic disease present
  – 2° Sjogrens: occurs in association with collagen vascular disease such as
    • RA and SLE
    • significant ocular/systemic manifestations

• New:
  – The diagnosis of SS should be given to all who fulfill the new criteria while also diagnosing any concurrent organ-specific or multiorgan autoimmune diseases, without distinguishing as primary or secondary.
Diagnosis: New Criteria

- Sjogren’s International Collaborative Clinical Alliance (SICCA) was funded by the National Institutes of Health to develop new classification criteria for SS

- New diagnostic criteria **requires at least 2 of the following 3:**
  - 1) positive serum anti-SSA and/or anti-SSB or (positive rheumatoid factor and antinuclear antibody titer >1:320),
  - 2) ocular staining score >3, or
  - 3) presence of focal lymphocytic sialadenitis with a focus score >1 focus/4 mm² in labial salivary gland biopsy samples
Ocular Surface Score (OSS)

- The ocular surface score (OSS) is the sum of:
  - 0-6 score for fluorescein staining of the cornea and
  - 0-3 score for lissamine green staining of both the nasal and temporal bulbar conjunctiva,
  - yielding a total score ranging from 0-12.
Antibodies to SS-A and SS-B

- Sjogren’s syndrome A and B
- Typically tested by ELISA and immunoblot
- Associated Conditions:
  - Uncommon in the normal population and in patients with rheumatic diseases other than Sjogren’s syndrome and SLE
  - Present in 75% of patients with “primart” Sjogren’s but only 10-15% of patients with RA and secondary Sjogren’s syndrome
Antibodies to SS-A and SS-B

• Indications:
  – Should be measured in patients with a clinical suspicion of Sjogren’s or SLE

• Interpretation:
  – Presence of AB’s is a strong argument for the diagnosis of Sjogren’s Syndrome in a patient with sicca syndrome
Dry Eye and Lid Disease?

• It is estimated that 67-75% of patients who have dry eye have some form of lid disease
  — it is often the most overlooked cause for dry eye symptoms

• Important to address the lids in any treatment plans for patients with dry eye
Case

- **23 WM**
  - Eye pain OD
  - Severe, started 2 days ago
  - Photophobia and redness
- **POHx:**
  - Had similar problem and was given drops and felt better
- **PMHx:**
  - Told to get back into shape and to reduce stress
- **Meds:**
  - Ibuprofen for lower back pain
Assessment

- VA: 20/20-, 20/20+
- Entrance skills unremarkable
- SLE:
  - OD:
    - 2+ injection,
    - 2+ cell,
    - Mild flare,
    - Fine deposits
  - IOP: 18, 14 mm HG
- DFE: unremarkable
HLA-B27 CONDITIONS
Ankylosing Spondylitis

- Ankylosing spondylitis is a type of arthritis that affects the spine:
  - symptoms include pain and stiffness from the neck down to the lower back.
- The vertebrae may grow or fuse together, resulting in a rigid spine.
  - these changes may be mild or severe, and may lead to a stooped-over posture.
Ankylosing Spondylitis

- Ankylosing spondylitis affects about 0.1% to 0.5% of the adult population.
- Although it can occur at any age, spondylitis most often affects men in their 20s and 30s.
  - It is less common and generally milder in women and most common in Native Americans.
- Early diagnosis and treatment helps control pain and stiffness and may reduce or prevent significant deformity.
Ankylosing Spondylitis

• Physical Exam:
  – The overall points taken into account when making an AS diagnosis are:
    • Onset is usually under 35 years of age.
    • Pain persists for more than 3 months (i.e. it is chronic).
    • The back pain and stiffness worsen with immobility, especially at night and early morning.
    • The back pain and stiffness tend to ease with physical activity and exercise.
    • Positive response to NSAIDs (nonsteroidal anti-inflammatory drugs).
Ankylosing Spondylitis

- **X-rays:**
  - The hallmark of AS is involvement of the sacroiliac (SI) joint
  - show erosion typical of sacroiliitis (inflammation of the sacroiliac joints).
  - can take 7 to 10 years of disease progression for the changes in the SI joints to be serious enough to show up in conventional x-rays.
Ankylosing Spondylitis

- HLA-B27 testing:
  - Generally speaking, no more than 2% of people born with this gene will eventually get spondylitis
  - it is important to note that the HLA-B27 test is not a diagnostic test for AS
  - the association between AS and HLA-B27 varies in different ethnic and racial groups.
  - over 95% of people in the caucasian population who have AS test HLA-B27 positive.
  - only 50% of African American patients with AS possess HLA-B27
  - close to 80% among AS patients from Mediterranean countries.
Ankylosing Spondylitis

• Treatment:
  – A common treatment regimen involves:
    • Medication (NSAIDs, Methotrexate, Anti-TNF),
    • exercise and possibly physical therapy,
    • good posture practices,
    • applying heat/cold to help relax muscles and reduce joint pain.
    • In severe cases surgery may also be an option.
Psoriatic Arthritis

- Psoriasis is a scaly rash that occurs most frequently on the elbows, knees and scalp, but can cover much of the body.
- It is a chronic, inflammatory disease of the skin, scalp, nails and joints.
- A normal skin cell matures and falls off the body's surface in 28 to 30 days, but a psoriatic skin cell takes only three to four days to mature and gathers at the surface, thus forming lesions.
Psoriatic Arthritis

• In 5-10% of those with psoriasis, arthritis also appears.
  – In most cases the psoriasis will precede the arthritis, sometimes by many years.

• When arthritis symptoms occur with psoriasis, it is called psoriatic arthritis (PsA).
  – the joints at the end of the fingers are most commonly affected
  – usually accompanied by symptoms of the fingernails and toes, ranging from small pits in the nails to nearly complete destruction and crumbling as seen in reactive arthritis or fungal infections.
Psoriatic Arthritis

- About 20% of people who develop PsA will eventually have spinal involvement, which is called psoriatic spondylitis.
- The inflammation in the spine can lead to complete fusion - as in ankylosing spondylitis - or skip areas where, for example, only the lower back and neck are involved.
- Those with spinal involvement are most likely to test positive for the HLA-B27 genetic marker.
- Up to 40% of people with PsA have a close relative with the disease, and if an identical twin has it, there is a 75% chance that the other twin will have PsA as well.
Psoriatic Arthritis

• Treatment for psoriasis remains suppressive, rather than curative.
  – Treatment of articular manifestations generally begins with non-steroidal anti-inflammatory agents (NSAIDs).
  – In patients with aggressive and potentially destructive disease, disease-modifying anti-rheumatic drugs (DMARDs) should be added early on in the course (Methotrexate, TNF-blockers, antimalarials).
Reactive Arthritis

- Reactive Arthritis (previously known as Reiter's Syndrome) is a form of arthritis that can cause inflammation and pain in the:
  - joints, the skin, the eyes, the bladder, the genitals and the mucus membranes.
- Reactive arthritis is thought to occur as a "reaction" to an infection that started elsewhere in the body, generally in the genitourinary or gastrointestinal tract.
Reactive Arthritis

• Reactive arthritis occurs after exposure / infection caused by certain types of bacteria. These include:
  – Chlamydia,
  – Bacteria such as Salmonella, Shigella, Yersinia or Campylobacter, which cause dysentery (diarrhea, abdominal pain, vomiting, fever).
    • Exposure to these bacteria occurs after eating spoiled or contaminated food.
• Not everyone exposed to these bacteria will contract ReA.
  – Those who go on to develop ReA tend to test positive for the HLA-B27 genetic marker, although other genetic factors may be involved.
  – Thus, it is an interaction between an individual's genetic make-up and the initial infection that causes Reactive Arthritis.
Reactive Arthritis

• ReA usually develops 2-4 weeks after the infection.
• A tendency exists for more severe and long-term disease in patients who do test positive for HLA-B27 as well as those who have a family history of the disease.
• Reactive Arthritis typically follows a limited course, where symptoms subsiding in 3-12 months.
• However, the condition has a tendency to recur.
• About 15-20% of people with ReA develop a chronic, and sometimes severe, arthritis or spondylitis.
Reactive Arthritis

• Treatment of reactive arthritis is based on where it has become manifest in the body.
  – For joint inflammation, patients are generally initially treated with NSAIDs.
  – Prednisone is used in the short-term treatment of inflammation in reactive arthritis
  – For the aggressive inflammation of chronic joint inflammation medications that suppress the immune system such as methotrexate
ReA Conjunctivitis

• Eye involvement occurs in about 50% of men with urogenital reactive arthritis and about 75% of men with enteric reactive arthritis.
• Conjunctivitis and uveitis can include redness of the eyes, eye pain and irritation, or blurred vision.
• Eye involvement typically occurs early in the course of reactive arthritis, and symptoms may come and go.
• Treatment includes NSAIDs and/or steroids.
Enteropathic Arthritis

• Enteropathic arthritis is a form of chronic, inflammatory arthritis associated with the occurrence of an inflammatory bowel disease (IBD):
  – the two best-known types of which are ulcerative colitis and Crohn's disease.

• About one in five people with Crohn's or ulcerative colitis will develop enteropathic arthritis.

• The most common areas affected by enteropathic arthritis are inflammation of the peripheral (limb) joints, as well as the abdominal pain and possibly bloody diarrhea associated with the IBD component of the disease.

• In some cases, the entire spine can become involved as well.
Enteropathic Arthritis

- The course and severity of enteropathic arthritis varies from person to person.
- The disease "flares" - the times when the disease is most active and inflammation is occurring - tend to be self-limiting, often subsiding after 6 weeks, but reoccurrences are common.
- In some cases the arthritis may become chronic and destructive.
Treatment

• A common treatment regimen for all the spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, enteropathic arthritis, and undifferentiated spondyloarthropathy) involves medication, exercise and possibly physical therapy, good posture practices, and other treatment options such as applying heat/cold to help relax muscles and reduce joint pain.

• In severe cases of ankylosing spondylitis, surgery may also be an option.
Treatment

• Medication
  – NSAIDs (nonsteroidal anti-inflammatory drugs) are still the cornerstone of treatment and the first stage of medication in treating the pain and stiffness associated with spondylitis.
  – However, NSAIDs can cause significant side effects, in particular, damage to the gastrointestinal tract.
  – When NSAIDs are not enough, the next stage of medications, (also known as second line medications), are sometimes called disease modifying anti-rheumatic drugs (DMARDs).
    • This group of medications include: Sulfasalazine, Methotrexate and Corticosteroids.
  – The most recent and most promising medications for treating ankylosing spondylitis are the biologics, or TNF Blockers. These drugs have been shown to be highly effective in treating not only the arthritis of the joints, but also the spinal arthritis. Included in this group are Enbrel, Remicade, Humira and Simponi