Autoimmune Diseases

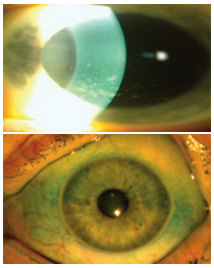
- Group of acquired diseases in which genetic factors appear to play a role
- They have in common widespread immunologic and inflammatory alterations of connective tissue
- The illnesses share certain clinical features and differentiation between them is often difficult because of this.
- Although thought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

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

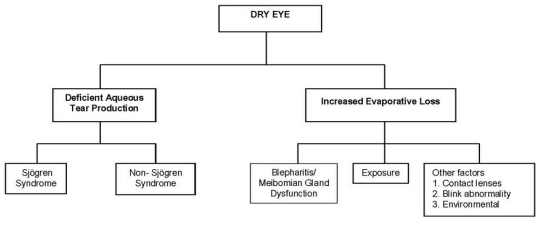
- VA (corrected):
  - OD/OS: 6/7.5 (20/25)
- PERRL
- EOM's: FROM
- CVF: FTFC
- SLE:
  - TBUT 5 sec OD, OS
  - Positive NaFl staining and Lissamine green staining of conj and cornea
  - Decreased tear prism



Additional Testing/Questions

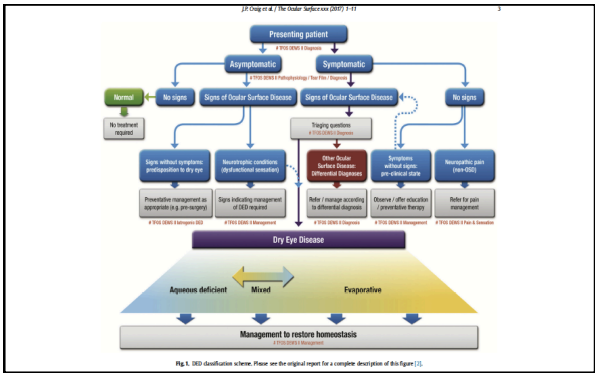
- Schirmer: < 5 mm of wetting in 5 minutes OD, OS
- RF (rheumatoid factor) and ANA (anti-nuclear antibodies): normal for patients age
- SS-A: 2.0 (normal < 1.0), SS-B: 1.9 (normal <1.0)
- Additional symptoms reported:
  - Patient experiences dry mouth and taking Salagen
- **Diagnosis: Sjogren Syndrome**

Differential Diagnosis of Dry Eye



DEWS 2: DED Definition

"Dry eye is a multifactorial disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by ocular symptoms, in which tear film instability and **hyperosmolarity**, ocular surface **inflammation** and damage, and **neurosensory abnormalities** play etiological roles."



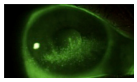
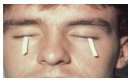
Signs and Symptoms of Dry Eye

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 (2 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

Role of Androgens?

- 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 3% promotes increased tear production and meibomian gland secretion, thereby reducing dry eye symptoms (Dr. Charles Connor).
- Progesterone 0.05%/Testosterone 0.05% Ophthalmic Solution BID (local compounding pharmacy?)
- **Topical Testosterone 0.5% drops BID (compounding pharmacy)**

Sjogren Syndrome

- Chronic AI disease that involves diffuse exocrine gland dysfunction and lymphocytic infiltration throughout the body
- Decreased lacrimal gland secretion results in K sicca
- Decreased salivary gland secretion results in sicca complex
- Emotional tearing is not affected

SJOGREN SYNDROME: OLD/NEW CLASSIFICATION

- Old:
  - 1º Sjogren: occurs when sicca complex manifests by itself
    - no systemic disease present
  - 2º Sjogren: 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.

Antibodies to SS-A and SS-B

- Sjogren Syndrome Antibodies 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 syndrome and SLE
  - Present in 75% of patients with "primary" Sjogren but only 10-15% of patients with RA and secondary Sjogren Syndrome

Antibodies to SS-A and SS-B

- Indications:
  - Should be measured in patients with a clinical suspicion of Sjogren or SLE
- Interpretation:
  - Presence of AB's is a strong argument for the diagnosis of Sjogren Syndrome in a patient with sicca syndrome

Sjogren Syndrome Ocular and Systemic

- Recently published article comments:
  - all patients had dry eye symptoms for approximately 10.4 years before presentation
  - 42% of the patients had systemic manifestations resulting from primary SS
  - **SS has been shown to be an independent risk factor for the development of non-Hodgkin' s lymphoma.**

Sjogren Syndrome Ocular and Systemic

- Authors recommendation:
  - primary SS is associated with vision- and life-threatening complications
  - presence of SS needs to be explored in patients with clinically significant dry eye because dry eye precedes the occurrence of the systemic manifestations

Dry Eye Summit

- Held in December 2014
  - Combination of optometrists, an ophthalmologist and industry
- Goal:
  - to find a way to encourage optometrists to look for, diagnose and manage dry eye in their patients
  - Come to a consensus on the minimum:
    - 3 questions that should be asked to identify dry eye patients
    - 3 diagnostic tests
    - 3 initial treatments

REV. as of March 13, 2015

Consensus on Screening Questions

1. Do your eyes ever feel dry or uncomfortable?
2. Are you bothered by changes in your vision throughout the day?
3. Are you ever bothered by red eyes?
4. Do you ever use or feel the need to use drops?

Recommendations from the ***Dry Eye Summit 2014***

Consensus on Baseline Diagnostic Options for Entry Level Dry Eye Disease

1. The lid
2. Staining
3. Tear stability

REV. as of March 13, 2015

Recommendations from the ***Dry Eye Summit 2014***

REV. as of March 13, 2015

Consensus on Baseline Management

1. For all patients:
   A. Ocular lubrication
   B. Lid hygiene
   C. Nutrition
2. Topical anti-inflammatories

Recommendations from the ***Dry Eye Summit 2014***

DREAM Study

- In a multicenter, double-blind clinical trial, we randomly assigned patients with moderate-to-severe dry eye disease to receive a daily oral dose of 3000 mg of fish-derived n−3 eicosapentaenoic and docosahexaenoic acids (active supplement group) or an olive oil placebo (placebo group).
- "The results of the DREAM study do not support use of omega-3 supplements for patients with moderate to severe dry eye disease"

DREAM Study

- In DREAM, most dry eye symptoms and signs appear to improve in both arms.
- In each trial group, there was a meaningful statistical change between baseline and 12 months (with time as a continuous variable) in the conjunctival staining score, the corneal staining score and the tear break-up time

Lifitegrast (Xiidra)

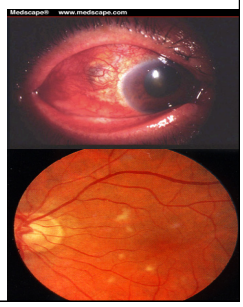
- Lifitegrast 5% (Xiidra) from Shire Pharmaceuticals approved by the FDA on July 11th, 2016
- indicated for the treatment of both signs and symptoms of dry eye disease
- Lifitegrast inhibits T-cell mediated inflammation associated with dry eye disease at several different points in the inflammatory cascade
- The most common side effects included irritation at the instillation site, dysgeusia and reduced visual acuity, reported in 5% to 25% of patients.

Case: Gonzalez

- 33 HF presents with a painful, red right eye
  - Started a couple of days ago, deep boring pain
  - Has tried Visine but hasn't helped the redness
- PMHx: patient reports she has been diagnosed with rheumatoid arthritis 3 years ago
  - Takes Celebrex for the joint pain
  - Patient reports she occasionally gets a skin rash when she is outdoors in the sun
- POHx: unremarkable
- PMHx: mother has rheumatoid arthritis

Case: Gonzalez

- VA:
  - 6/7.5 (20/30) OD,
  - 6/6 (20/20) OS
- Pupils: PERRL –APD
- VF: FTFC OH
- EOM's: FROM OU
- BP: 130/85 mm Hg RAS
- SLE: see picture
  - 2+ cells, mild flare
- IOP's: 16, 16 mm HG
- DFE: see fundus photo

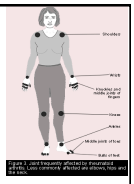


Patient Update

- Patient was worked up for lupus and diagnosed with lupus.
- Patient was already taking Celebrex which was not effective in treating the scleritis she presented with
  - upon referral to rheumatology it was discovered that she had several organs already being affected by the lupus
  - she was put on immunosuppressive agents to treat the systemic and ocular manifestations
- Patient was taken off of Celebrex and put on plaquenil (hydroxychloroquine) 400 mg po qd

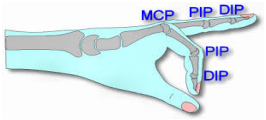
RHEUMATOID ARTHRITIS

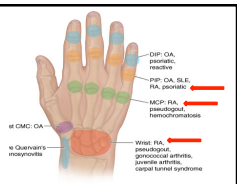
RA Epidemiology



- Affects ~1% of the US population
- **Female** 3:1
- Most common age of onset: 50-75 years
  - though patients 35-50 may have early symptoms
- Lower prevalence in African Americans & Chinese (more common in Native Americans)
- **Smoking and obesity are risk factors***
- Genetic association (familial predisposition)
  - HLA-DR4 and HLA-DRB present in 50-75% of cases

RA presentation



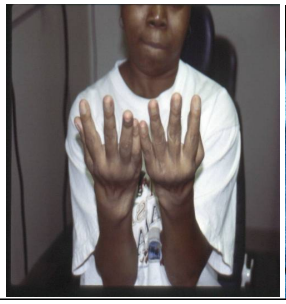


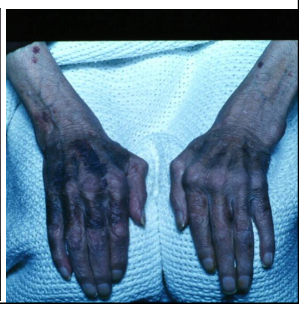
- Slow, **symmetric** polyarthritis
- Pain, stiffness, swelling, limited movement in the **small peripheral joints** (**hands**, **wrist**, ankle, feet). Can progress to larger joints and organs
- Other symptoms: Weight loss, fatigue, fever, malaise

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.
- 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 infl' n 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

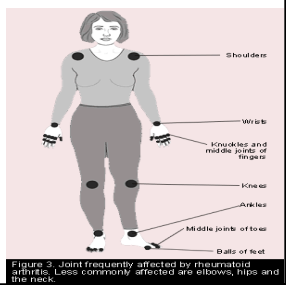
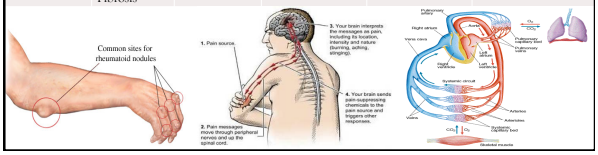


Figure 3. Joint frequently affected by rheumatoid arthritis. Less commonly affected are elbows, hips and the neck.

Other Diagnostic Criteria for RA

Cutaneous	Ocular	Pulmonary	Cardiac	Neurological	Hematological
Nodules	Sicca	Pleuritis	Pericarditis	Peripheral neuropathy	Leukopenia
Vasculitis	Episcleritis	Nodules	Atherosclerosis	Cervical myelopathy	Anemia of chronic disease
	Scleritis	Interstitial lung disease	Myocardial infarction		Lymphadenopathy
	Fibrosis				



Osteoarthritis (OA) vs. RA

- Etiology of RA is inflammatory which improves with activity while osteo is mechanical and worsens with activity
- Infl' n 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

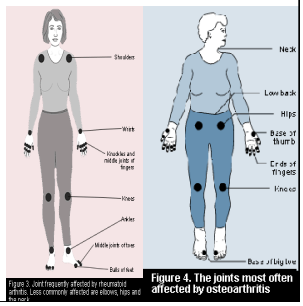
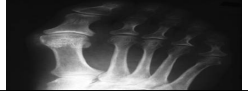


Figure 4. The joints most often affected by osteoarthritis

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

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

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 (ACPA)

- Proteins that contain citrulline are the target of an AB response that is highly specific for RA
- 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
    - **80-97% of pts have RA if they are RF+ and ACPA+**

Antibodies to Cyclic Citrullinated Peptides (anti-CCP)

Indication:

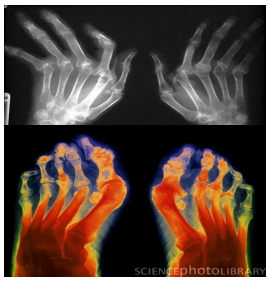
- Should be ordered when there is a clinical suspicion of RA

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.
- There is no curative treatment for RA
  - treatment is to minimize inflammation
  - minimize damage and
  - maximize patient functioning

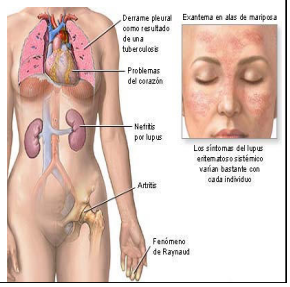
Treatment and Management-Systemic

- 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

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

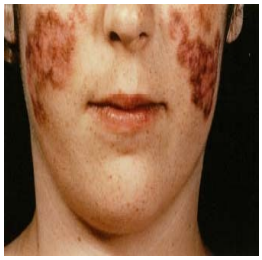
- SLE is not uncommon with prevalence exceeding 1:2000 persons with 85% being female
- Disease may occur at any age though most patients are b/w ages 20-40
  - AA being affected 3x more than any other race (and more severely)

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.

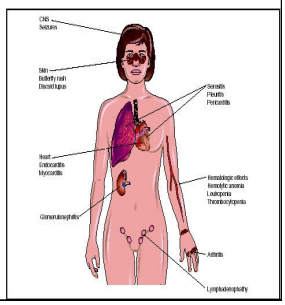
Diagnosis

- 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 Rheumatolgy 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

Rheumatic Diseases	Organ-Specific AI Diseases	Other
SLE	AI thyroid disease	Drug-induced lupus
Mixed connective tissue disease	AI hepatitis	Asymptomatic drug-induced ANA
Scleroderma	Primary biliary cirrhosis	Chronic infections
Sjogren syndrome	AI cholangitis	Idiopathic pulmonary fibrosis
RA		Primary pulmonary hypertension
Polymysositis		Lymphoproliferative disorders
Dermatomyositis		Type 1 diabetes (ketoacidosis)
Discoid Lupus		

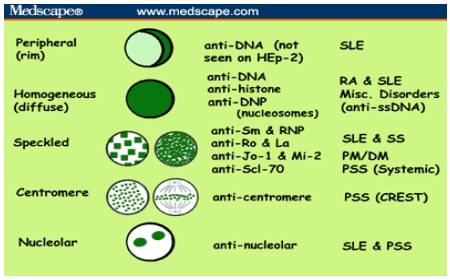
Lab Tests: Antinuclear Antibodies (ANA)

- 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

ANA Staining Patterns



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 been reported to be virtually 100% predictive
- Decreased serum complement levels result from activation and consumption of complement components

"New" Lab Tests

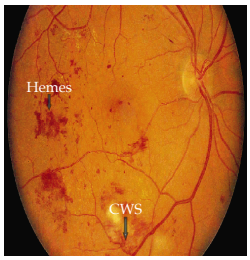
- Anti Sm is found almost exclusively in people with lupus.
  - It is present in 20% of people with the disease
  - rarely found in people with other rheumatic diseases and its incidence in healthy individuals is less than 1%
- Anti-RNP antibodies are commonly found along with anti-Sm antibodies in people with SLE.
  - The incidence in lupus is approximately 25%, while less than 1% of healthy individuals possess this antibody.
- Anti-Ro/SSA and Anti-La/SSB are antibodies found mostly in people with systemic lupus (30-40%) and primary Sjogren's syndrome.
  - They are also commonly found in people with lupus who have tested negative for anti-nuclear antibodies.

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 (Plaquenil) 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

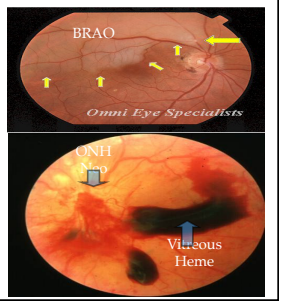
Ocular Manifestations

- 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



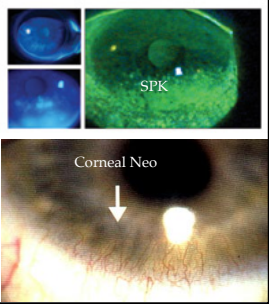
Ocular Manifestations

- 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