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Autoantibodies and Rheumatologic Diseases: When and How to Use Laboratory tests

Seetha Monrad M.D.

Fall 2009



Case 1

- 23 year old woman is referred to your clinic to “rule out lupus”
- History is notable for no photosensitivity, unusual rashes, oral ulcers, pleurisy, hair loss, or arthralgias
- On family history, has an aunt with Sjögren’s disease and a cousin with lupus
- Physical exam completely within normal limits
- Outside labwork: ANA 1:40
- Does she have SLE?

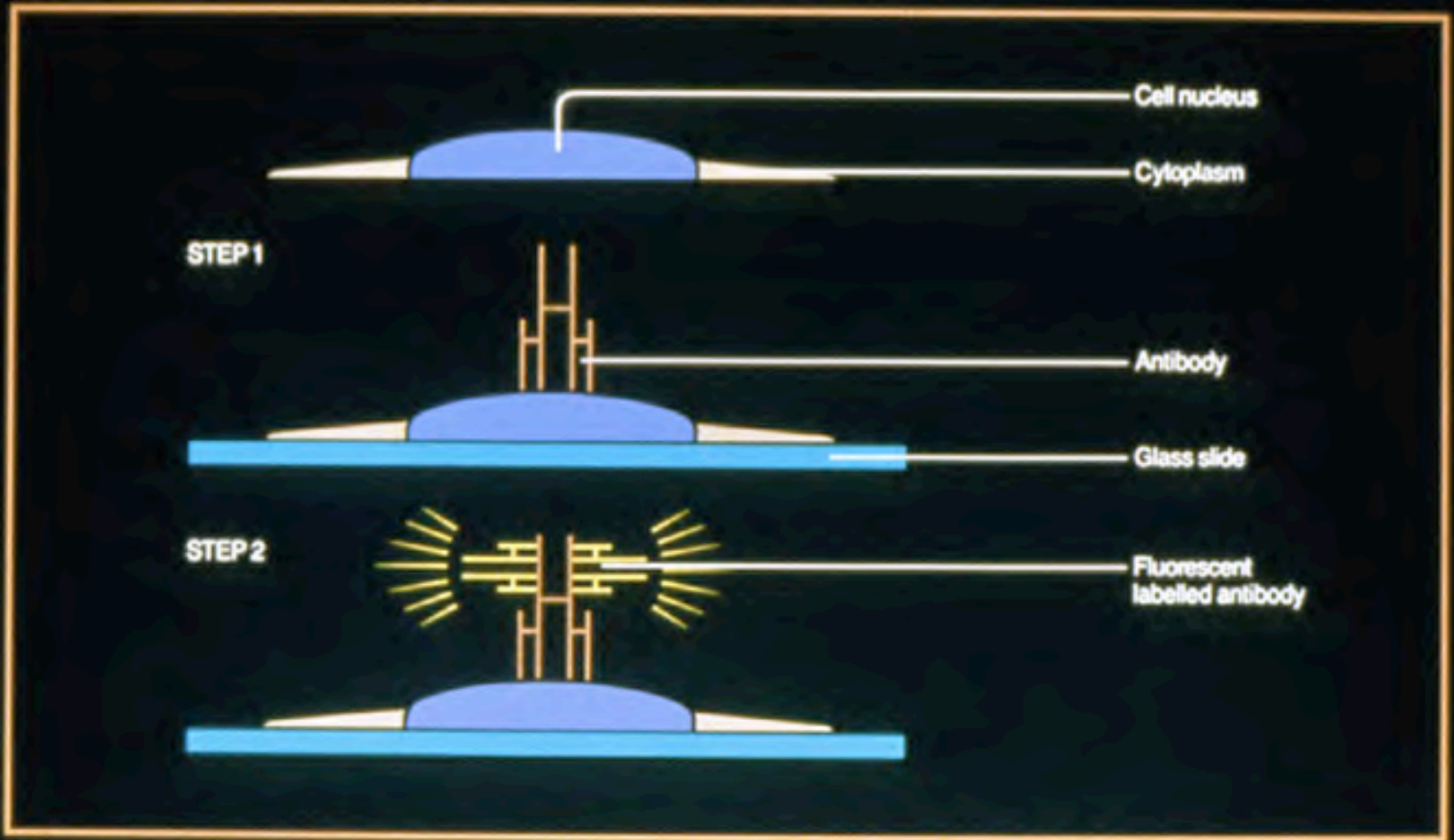
Autoantibodies

- Autoantibodies are immunoglobulins that bind to antigens originating in the same individual or species (autoantigens)
- Autoantigens include self molecules in the nucleus, cytoplasm, and cell surface
- Many autoantibodies are **associated** with autoimmune diseases but the majority of autoantibodies have **no known pathogenic role** in any disease

Antinuclear antibodies (ANA)

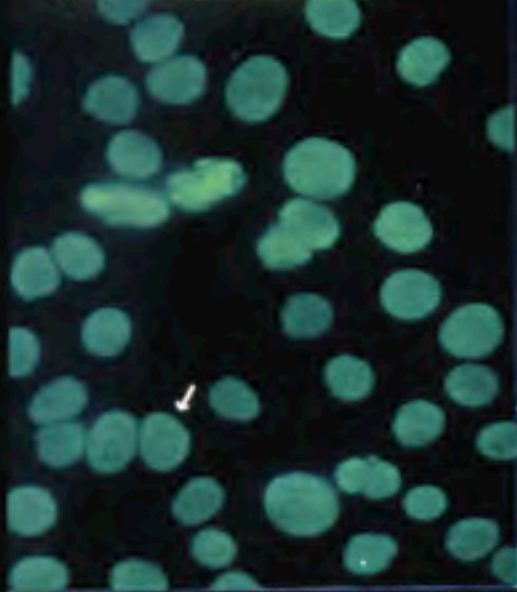
- Serologic hallmark of autoimmune diseases
- May bind DNA, RNA, nuclear proteins, protein-nucleic acid complexes

Principle of Indirect Immunofluorescence



Adapted from American Rheumatism Association Glossary Committee: *Dictionary of the Rheumatic Diseases*, vol II, Diagnostic Testing. Contact Associates, 1985, p 17.

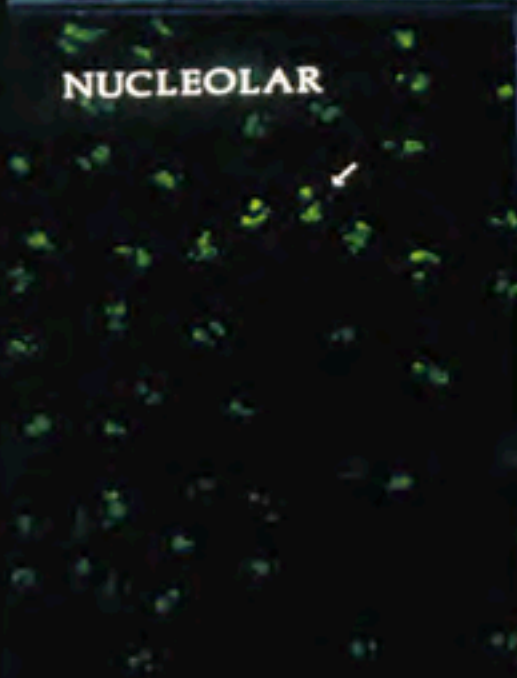
HOMOGENEOUS



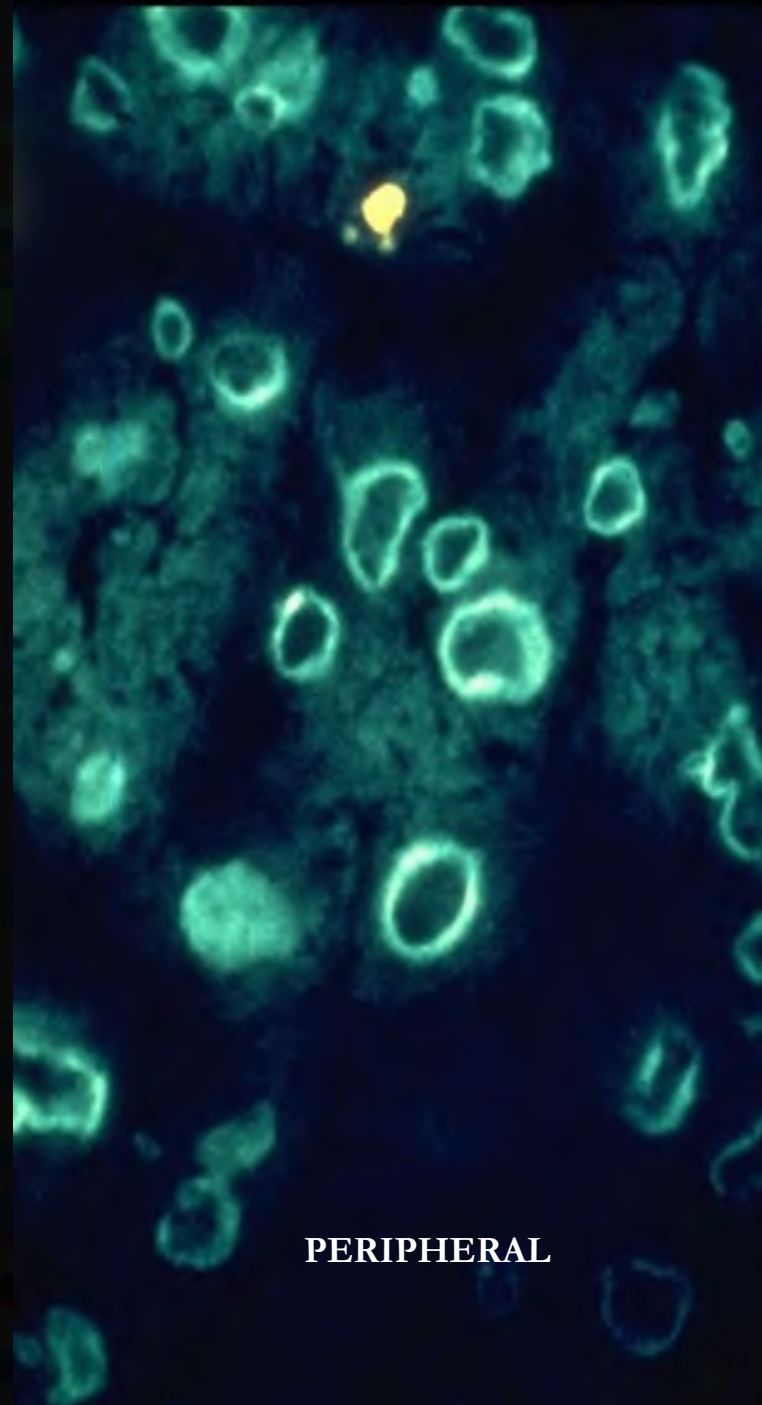
SPECKLED



NUCLEOLAR



CENTROMERE



PERIPHERAL

ANA in non-rheumatologic diseases

- Hashimoto's thyroiditis 40-50%
- Graves' disease 50%
- Autoimmune hepatitis 60-90%
- Primary biliary cirrhosis 10-40%
- Chronic infectious diseases
 - Mononucleosis
 - Hepatitis C
 - Subacute bacterial endocarditis
 - TB
- **Normal Population 5%**
 - Higher in women, elderly

ANA in rheumatologic diseases

- SLE
- Drug-induced SLE
- RA (40%)
- Polymyositis/dermatomyositis (75%)
- What else?

Case 2

- A 40 year old woman presents with “hand pain”
- 6 months ago noted fingers changing colors, associated with pain
- Two months ago fingers became diffusely swollen, painful, difficult to move
- Noticing a little difficulty breathing



PD-ENEL American College of Rheumatology



PD-ENEL Source Undetermined

Systemic sclerosis

- Generalized disorder of connective tissue
- Characterized clinically by thickening and fibrosis of the skin (scleroderma)
- Distinctive forms of involvement of internal organs, notably the heart, lungs, kidneys, and gastrointestinal tract
- *scleroderma* (Greek *skleros* ["hard"] + *derma* ["skin"])

“Scleroderma is one of the most terrible of all human ills. Like Tithonus to “wither slowly”, and like him to be “beaten down, and marred and wasted” until one is literally a mummy, encased in an ever shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern.”

- Osler, 1898

Classification

- ***With diffuse cutaneous scleroderma***
 - Skin thickening present on the trunk in addition to face, proximal and distal extremities
- ***With limited cutaneous scleroderma***
 - Skin thickening limited to sites distal to the elbow and knee but also involving the face and neck
 - Synonym: CREST syndrome (C, calcinosis; R, Raynaud's phenomenon; E, esophageal dysmotility; S, sclerodactyly; T,

Raynaud's phenomenon



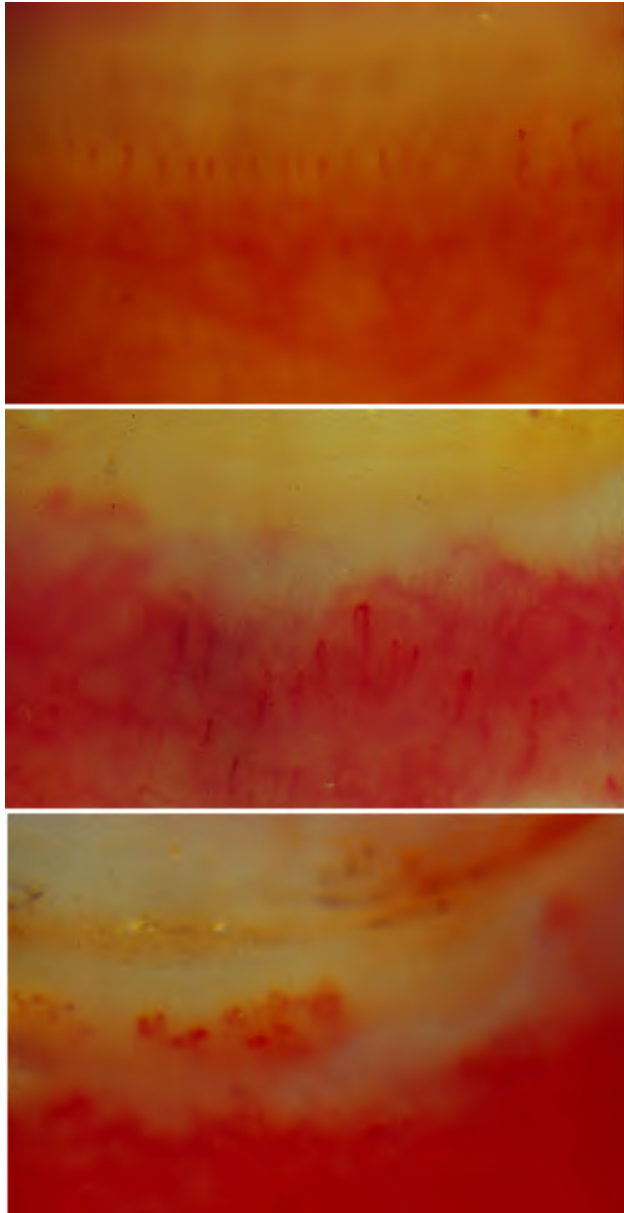
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Triphasic color change: white, blue, red

Primary: common, benign, affects young women, precipitated by cold/stress

More likely to be secondary (pathologic) with: older age at onset, few fingers involved, prolonged painful ischemic episodes, abnormal nailfold capillary exam



Nailfold capillaroscopy

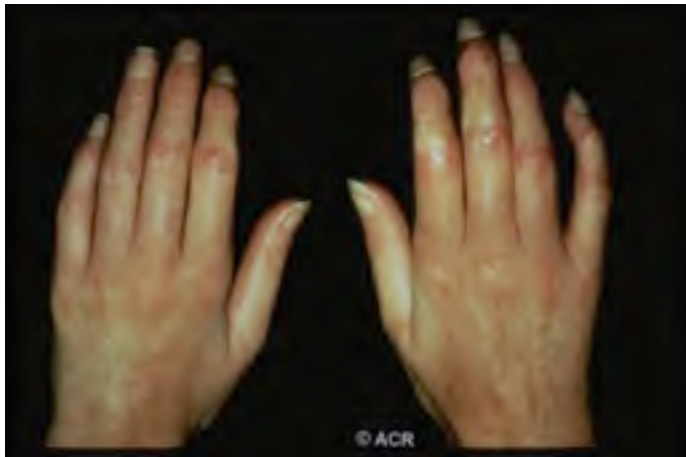
- Top: normal symmetric hairpin loops.
- Center:
 - tortuosity and redundancy of multiple capillary loops
 - might be encountered in both systemic sclerosis and other connective tissue disorders
- Bottom: disease-specific changes of systemic sclerosis, including a paucity of capillary loops (drop-out) and grossly dilated loops

Sclerodactyly

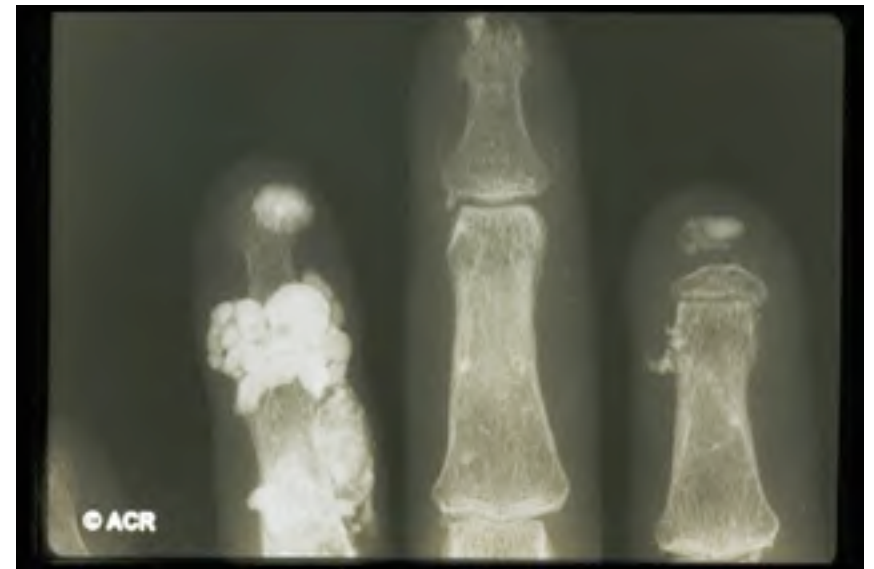


Source Undetermined

Digital ischemia



Calcinosis cutis



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Cutaneous findings



Vasculopathy



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Marked intimal hyperplasia
causing luminal occlusion



PD-INEL Source Undetermined

Scleroderma renal crisis: used to be most
feared complication and major cause of
mortality – less common now

Pulmonary fibrosis and pulmonary hypertension



Gastrointestinal manifestations



Systemic Sclerosis

Autoantibodies

- **ANA:** 85%
- **Anti-centromere:** limited cutaneous
- **Anti-Scl-70:** diffuse scleroderma

Treatments

- GERD: PPI, non-drug therapies
- GI dysmotility: prokinetics
- Alveolitis: steroids, immunosuppressives
- Pulm HTN: similar to idiopathic
- Renal: ACE inhibitors

Raynaud's phenomenon

- Treatment
 - Behavioral modification
 - Warm extremities AND core
 - Avoid smoking
 - Medications
 - Calcium channel blockers (felodipine, amlodipine)
 - ACE-inhibitors, angiotensin receptor blockers
 - Selective serotonin reuptake inhibitors
 - Phosphodiesterase inhibitors (sildenafil)
 - Topical nitrates
 - For severe (digital ischemia):
 - Iloprost (intravenous prostacyclin agonist)
 - Bosentan (endothelin receptor blocker)
 - Sympathetic block/ sympathectomy

Case 4

- A 60 year old woman comes to clinic to establish care
- No major complaints
- On careful ROS, you elicit that she often feels like she has gravel in her eyes, and uses eye drops four times a day
- She also has a history of numerous dental caries
- Exam:
 - Parotid gland enlargement
 - Conjunctival erythema
 - Extremely dry oral mucosa

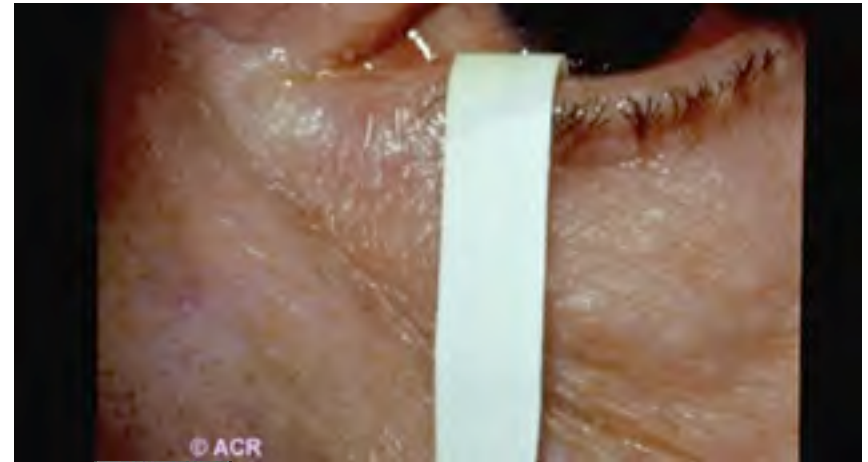


Sjögren's Syndrome

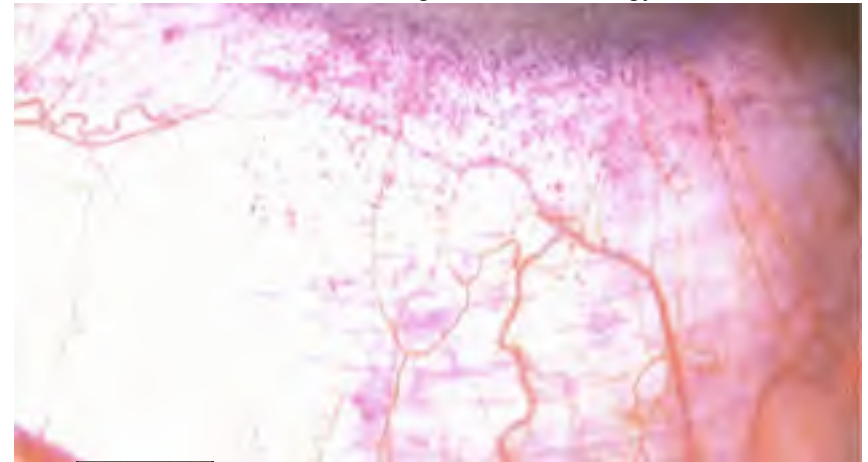
- Affects 500,000 to 2 million people in US
- A major women's health issue
- Of increasingly important in an aging population
- Often overlooked and neglected
- Holds clues for both autoimmunity and cancer
- Dry mouth and dry eyes (oral and ocular sicca)
- Extraglandular manifestations
- Overlap with other diseases
 - Rheumatic: RA, SLE
 - Thyroiditis, primary biliary cirrhosis, multiple sclerosis
 - Hepatitis C
- Lymphoproliferative disorder

Sjögren's Syndrome: Ocular manifestations

- Foreign body sensation, like sand in eyes
- Inability to tolerate contact lenses
- Redness, ocular fatigue
- Thick mucous strands in the morning
- Objective: Schirmer's testing, Rose-Bengal staining

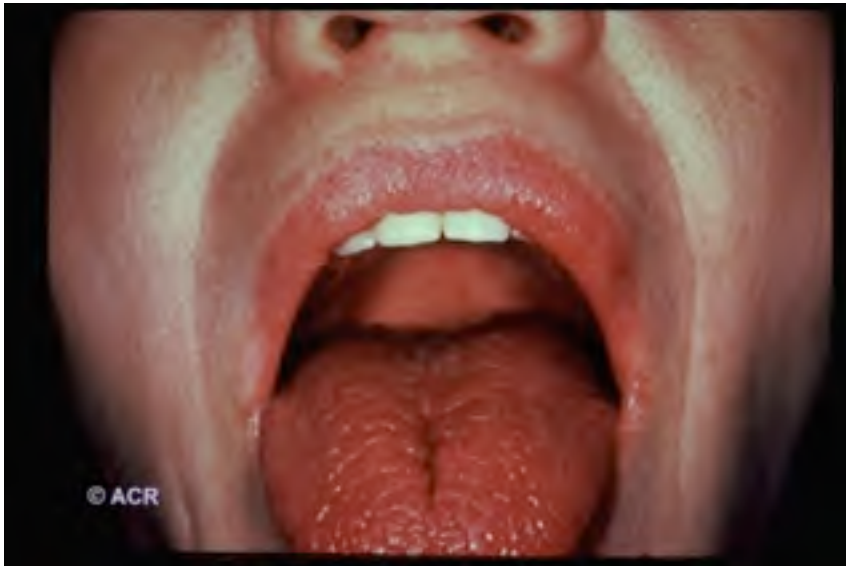


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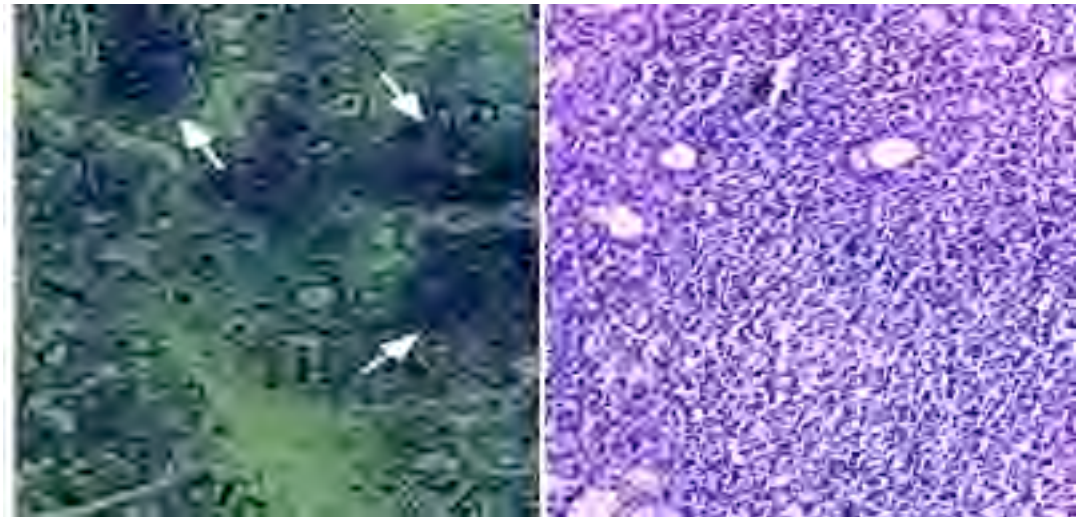
Sjögren's Syndrome: Oral manifestations



- Dry mouth; carry water bottles, water at bedside
- “Cracker sign”: unable to eat dry food without liquid
- Poor dentition; unable to wear dentures
- Oral candidiasis

Classification Criteria for Sjögren's Syndrome*

- I Ocular symptoms
- II Oral symptoms
- III Ocular signs
- IV Histopathology
- V Salivary gland involvement
- VI Autoantibodies



*The presence of 4 out of 6 criteria, including 1 objective criterion (histopathology or autoantibodies). Exclusions include HIV infection, lymphoma, GVHD, sarcoidosis.

Autoantibodies in Sjogren's syndrome

- **ANA:** ~67%
- **Anti Ro/SSA:**
 - Recognize cellular proteins with M.W. ~52-60kDa
 - Associated with Sjogren's (75% primary, 15% secondary), SLE (50%)
 - Subacute cutaneous lupus, neonatal lupus and congenital heartblock
 - 0.1-0.5% normal adults
- **Anti-La/SSB:**
 - Almost always associated with anti-Ro (except in primary biliary cirrhosis and autoimmune hepatitis)
 - Associated with Sjogren's (40%), SLE (15%), and neonatal lupus

Anti-Ro/La and Neonatal Lupus Syndromes

- From transplacental passage of maternal anti-Ro/La in the perinatal period
- Transient rash
- Congenital heart block
 - ~1% rate of CHB in Ro +ve mothers
 - ~15% rate of CHB in second child
- most often identified between 18-24 wks gestation
- ~50% of asymptomatic mothers with children who have neonatal lupus will eventually develop an autoimmune disease such as lupus or Sjogren's



Treatment of Sjögren's Syndrome

- Ocular manifestations
 - Artificial tears
 - Punctal plugging
 - Topical cyclosporine
- Oral sicca
 - Good dental hygiene
 - Avoid anticholinergic drugs
 - Saliva substitutes
 - Stimulate salivary flow
 - Sugar free candy/gum
 - Muscarinic agonists
 - Treat oral candidiasis
- NSAIDs
- Corticosteroids
- Hydroxychloroquine
- Immunosuppressives
e.g. methotrexate,
cyclophosphamide

Back to case 1....

- 23 year old woman is referred to your clinic to “rule out lupus”
- History is notable for no photosensitivity, unusual rashes, oral ulcers, pleurisy, hair loss, or arthralgias
- On family history, has an aunt with Sjögren’s disease and a cousin with lupus
- Physical exam completely within normal limits
- Outside labwork: ANA 1:40
- Patient does not have lupus
- ANA is low titer; likely false positive
- Alternately, may reflect autoimmunity in her family

Case 4

- The same woman returns two years later, complaining of fatigue, arthralgias
- ANA drawn 2 weeks ago was >1:2560
- What lab would be consistent as part of a diagnosis of lupus?
 1. Anti-Ro Ab
 2. Anti-phospholipid Ab
 3. Anti – dsDNA
 4. Anti – Sm
 5. Low C3

Specific antinuclear antibodies

- Anti- dsDNA antibodies
 - Highly specific for SLE
 - Specific assays
 - Farr
 - Crithidia
 - Levels fluctuate over time
 - Serum levels may correlate with renal disease activities
 - Have been isolated from glomerular elutes from patients with active nephritis →?
Pathogenic

Specific antinuclear antibodies

- ENA: extractable nuclear antigens
 - Anti-Sm
 - Smith antigen: snRNP (small nuclear ribonucleoprotein) core proteins
 - Highly specific for SLE; sensitivity 30%
 - Levels remain fairly constant and do not fluctuate with disease activity
 - Anti-RNP
 - Present in SLE (30-40%)
 - High titers → mixed connective tissue disease

Anti-Histone Antibodies

- >95% cases of drug-induced lupus
 - Procainamide
 - Hydralazine
 - Phenytoin
 - Isoniazid
- Also seen in idiopathic SLE (70%)

Anti-Phospholipid (APL) Antibodies

- Can be ‘primary’ or associated with a connective tissue disease e.g. SLE
- 4 subtypes
 - False positive VDRL
 - Lupus anticoagulants
 - Anticardiolipin antibodies
 - Anti- β 2-glycoprotein antibodies
- Associated with arterial/venous thrombosis, recurrent fetal loss, thrombocytopenia

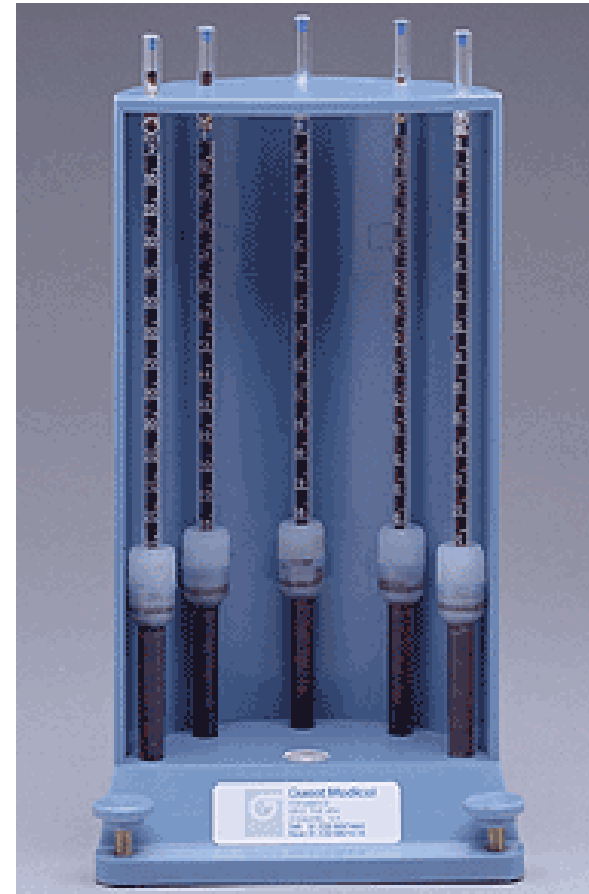
Clinical use of complements in SLE

- C3, C4
- Low levels can indicate active disease
- Don't order CH50; screens for deficiency in complement cascade
- Low complements can also be seen in other conditions (cryoglobulinemic vasculitis, Sjogren's etc.)

Other labs often ordered

Erythrocyte sedimentation rate (ESR)

- The rate (mm/hr) at which anticoagulated blood settles in a special tube (Westegren tube)
- Estimate for normal value:
= $\frac{[\text{age}(\text{yrs}) + 10 \text{ (if female)}]}{2}$
- Inflammation → increased plasma proteins and fibrinogen (acute phase reactants)
→ cause RBCs to stick together and fall faster → higher ESR



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ESR

- Indirect marker of inflammation
 - dependent on
 - size, shape and number of RBCs
 - presence of other plasma components (ie immunoglobulins)
 - Affected by
 - age and gender
 - Responds slowly to inflammatory stimuli

Inflammatory markers

- Acute phase proteins
 - Produced by hepatocytes
 - Acute phase response: increase in serum proteins in response to cytokine release (esp. IL-6) from monocytes and macrophages in inflammatory states
 - CRP:
 - Precise function unknown; activates complement, but also anti-inflammatory
 - Rapidly fluctuates in response to inflammation
 - Others: serum amyloid A (SAA), ferritin

Summary

- Autoantibodies are confirmatory but rarely diagnostic
- Often are epiphenomena
- Know which lab abnormalities tend to be present in different diseases, but don't rely on them exclusively

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Slide 7: Adapted from American Rheumatism Association Glossary Committee: Dictionary of the Rheumatic Diseases, vol II, Diagnostic Testing.
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Slide 15: Journal of Musculoskeletal Medicine

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