Recognition and Appropriate Work-Up of the Patient with Rheumatic Disease Prior to Rheumatology Referral: *A Joint Effort*

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INTRODUCTION

PATIENT

- 1/7 visits are for a MSK complaint
- Patient wants relief
- Patient wants an explanation

PRIMARY CARE PROVIDER

- Is this a systemic process or a localized issue?
- Do I embark on a lab work-up?
- Do I "keep" or "send"
- NSAID and film ??

OVERVIEW OF TALK

- "Rheum History", Pattern
- "Rheum Review of Systems"
- Focused Physical Examination
- Laboratory Evaluation
- Imaging
- Pattern Recognition
- The Elderly
- Management (brief, PEARLS)

THE RHEUMATOLOGIC HISTORY
Arthralgia vs. Arthritis

JOINT PATTERN

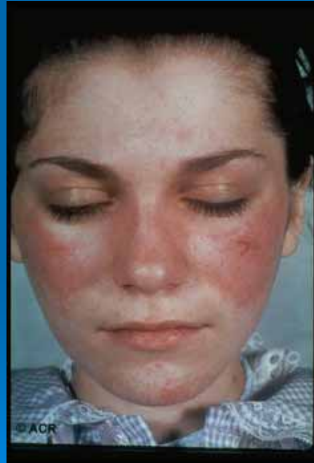
- Location (joint or periarticular structure)
- Inflammatory vs. noninflammatory
  - Worse or better with activity vs. rest?
- Additive?
- Migratory?
- Acute vs chronic?
- Number of involved joints
  - Monoarthralgia/arthritis
  - Oligoarthalgia/arthritis [up to 4]
  - Polyarthalgia/arthritis [5 and up]

JOINT PATTERN

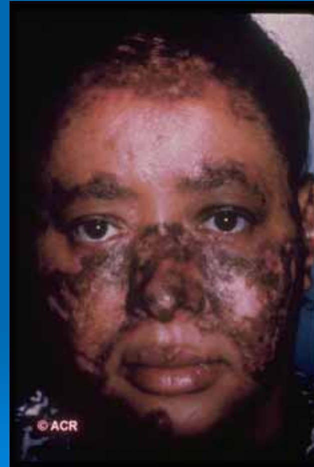
- Site /distribution of affected joints
  - Axial or peripheral
  - Symmetric or asymmetric
- Presence or absence of enthesopathy – suggestive of the SNSA's (AS, PsA, Reiter's/Reactive, IBD associated)
  - Dactylitis ("sausage digit")
  - Enthesitis or tendinitis
- Worse in the morning? Better with activity? = inflammatory

The "Five" Minute Rheumatologic Review of Systems (ROS)

ROS - RASH

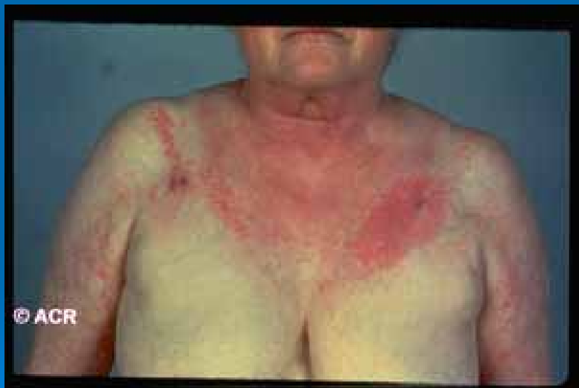


Acute Cutaneous Lupus



Discoid Lupus

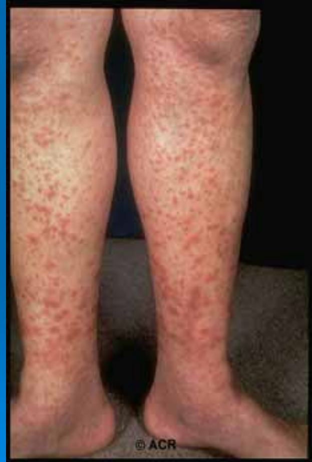
ROS - RASH



Dermatomyositis

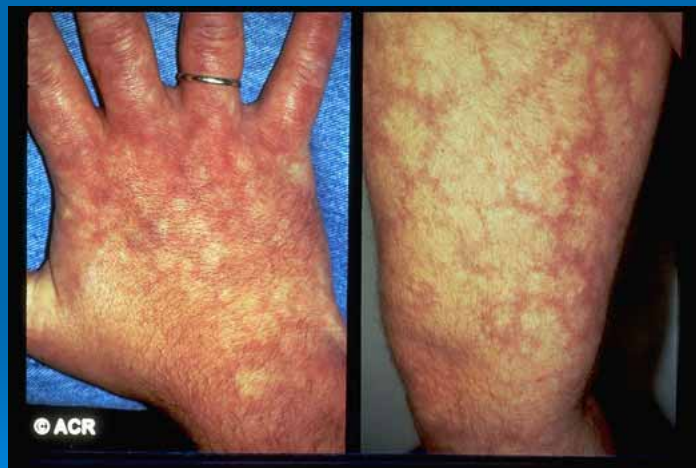
Heliotrope rash

ROS - RASH



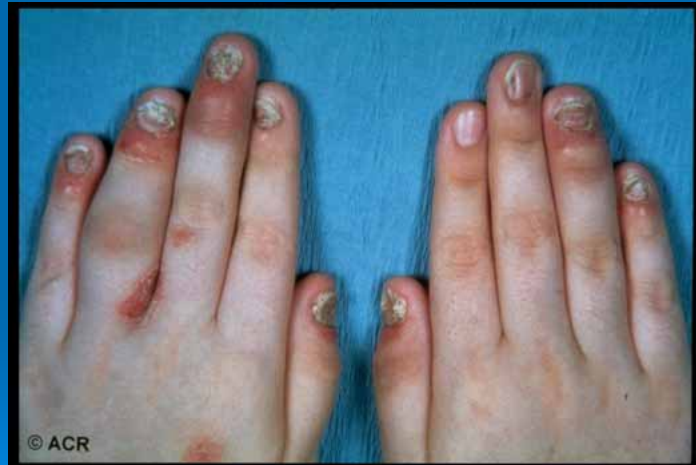
Palpable purpura - HSP

ROS - RASH



Livedo reticularis – APLA Syndrome vs vasculitis

ROS - PSORIASIS



Psoriatic arthritis

ROS - RASH

Circinate Balanitis in Reactive arthritis

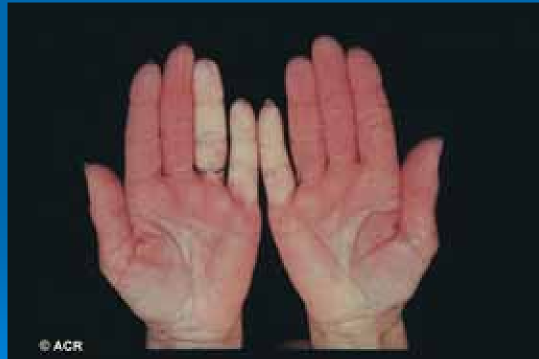
ROS - CONJUNCTIVITIS

Reactive arthritis

ROS - UVEITIS

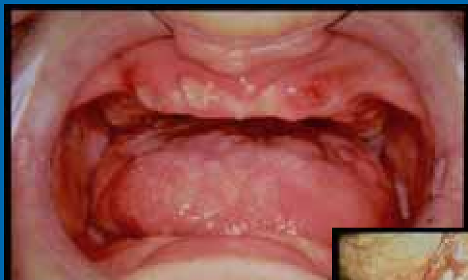
Behcet's
SNSA's

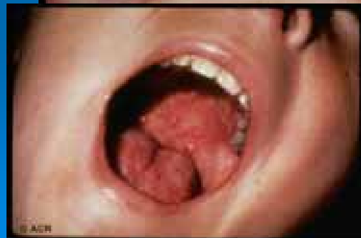
ROS - RAYNAUD'S



Scleroderma
SLE
DM/PM
MCTD

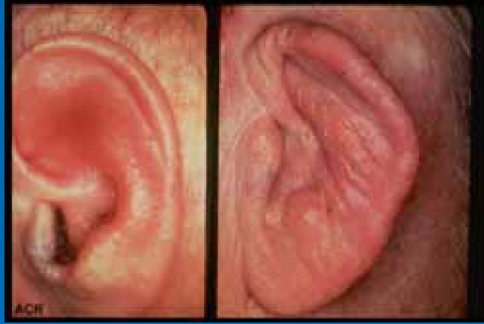
ROS – ORAL/GENITAL ULCERS

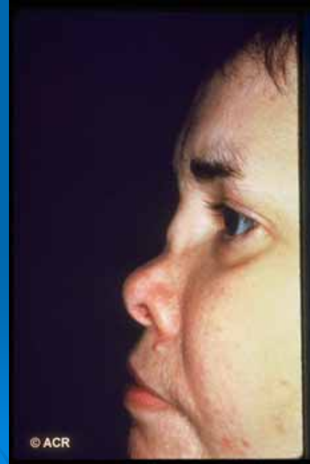




SLE
Behcet's

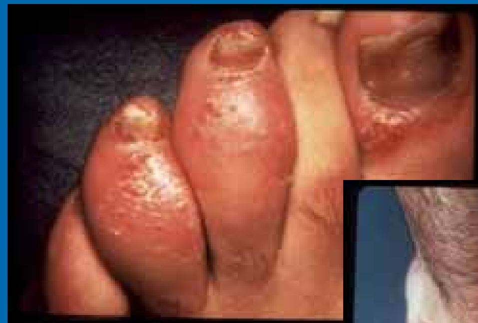
ROS - POLYCHONDRITIS

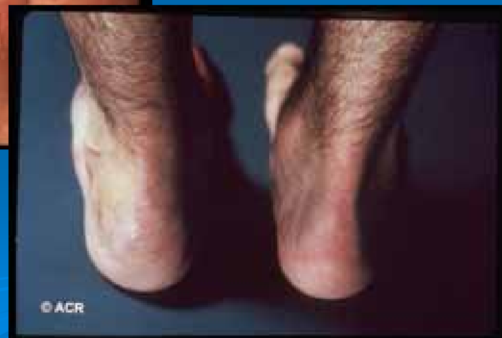




Relapsing polychondritis

ROS-ENTHESOPATHY

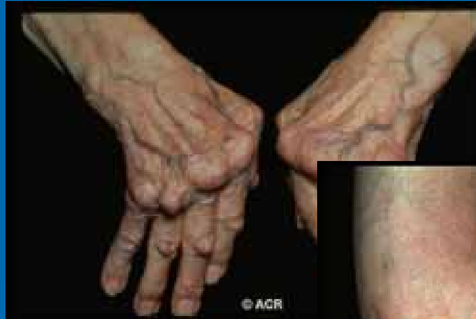


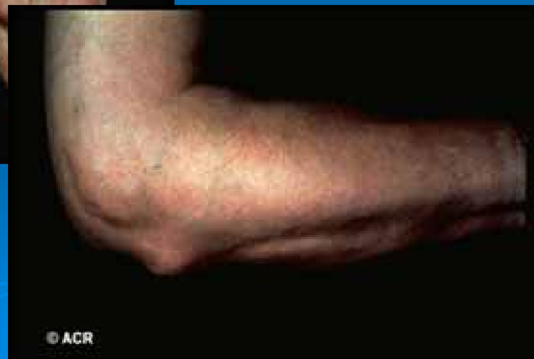


SNSA's:

- Reiter's
- AS
- Psoriatic
- IBD

ROS - NODULES





RA
Gout

OTHER ROS

- IBD symptoms
- infectious diarrhea or STD sx preceding
- photosensitivity
- hypercoagulable event
- Recurrent pregnancy loss?
- heme/renal/CNS or PNS disease
- Sicca (ocular, oral)
- Pleuropericarditis (lupus, Still's, RA)

AGE

- 1-15 yo
  - JCA
  - Still's
  - Acute Rheumatic Fever
- 20-45 yo
  - SLE / RA
  - SNSA's
  - PM/DM
  - Disseminated gonnococcal infection
  - Vasculitis

AGE

- 45-60 yo
  - Crystalline (MSU, CPPD)
  - Osteoarthritis
  - Sjogren's
- 65 +
  - PMR
  - GCA
  - Crystalline (CPPD, MSU, others)
  - Dermatomyositis (THINK Malignancy)

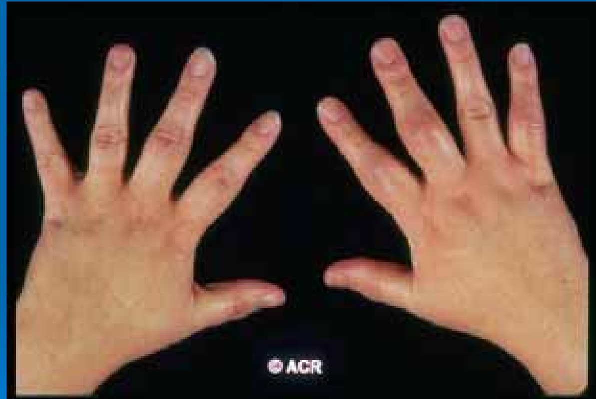
GENDER

MEN	WOMEN
- MSU crystals (gout)	- RA
- OA of knees	- SLE
- AS	- Sjogren's
- Reactive (Reiter's)	- OA of fingers

FAMILY HISTORY

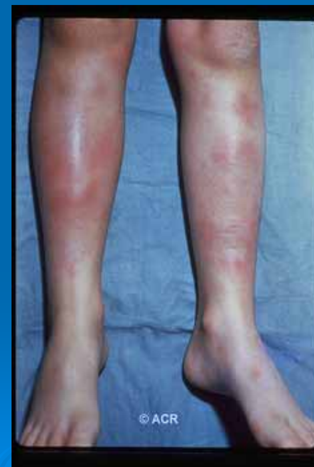
- Nodal osteoarthritis
- SLE
- RA

PATTERN RECOGNITION ACUTE



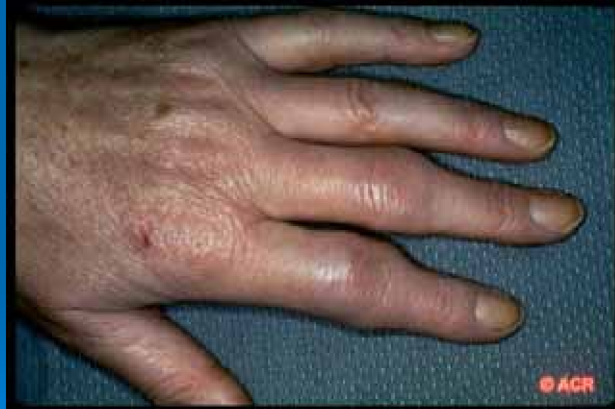
Parvovirus infection

PATTERN RECOGNITION ACUTE



Sarcoid / Lofgren's Syndrome

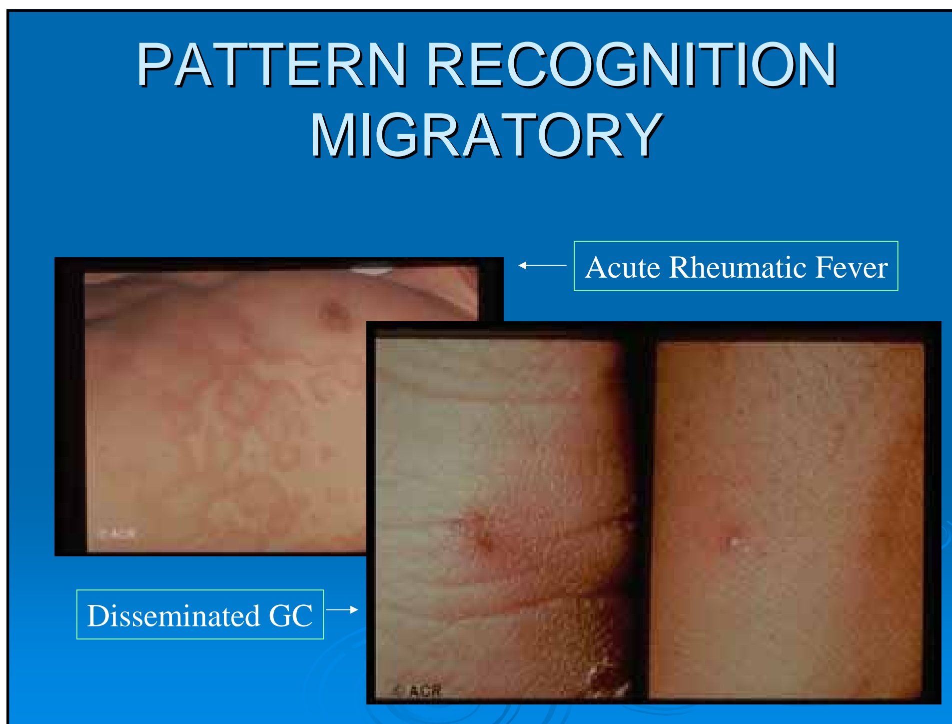
PATTERN RECOGNITION INDOLENT



Rheumatoid arthritis

PATTERN RECOGNITION BRIEF & RELAPSING

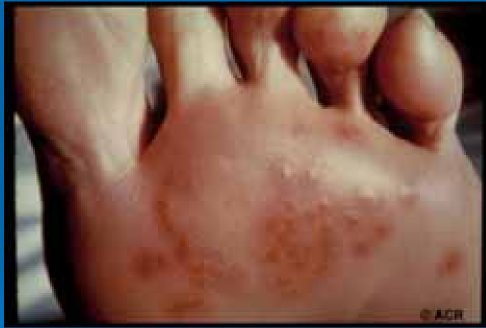
SLE

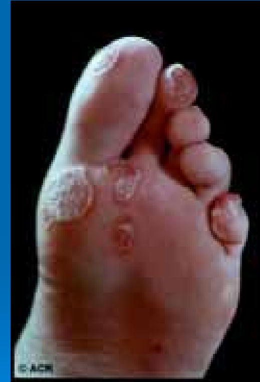


"FOCUSED" FIVE MINUTE PHYSICAL EXAM (PE)

- alopecia
- nasal / genital / oral ulcers
- rash
- synovitis – joint inflammation
- cutaneous vasculitis
- adenopathy / HSM
- enthesitis
- dactylitis
- xerostomia
- mononeuritis multiplex
- pleuropericarditis

PE - RASH



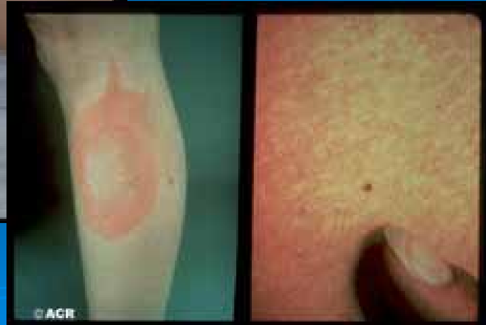


Keratodermia blenorrahgica – Reactive arthritis

PE - ALOPECIA

SLE

PE - RASH

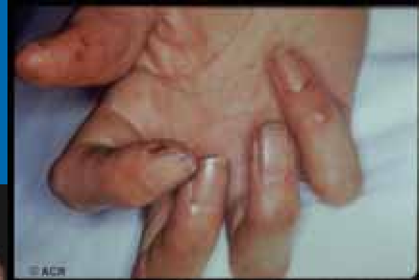


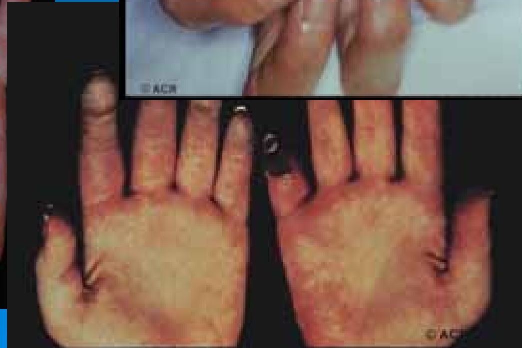
ECM - Lyme

PE - RASH

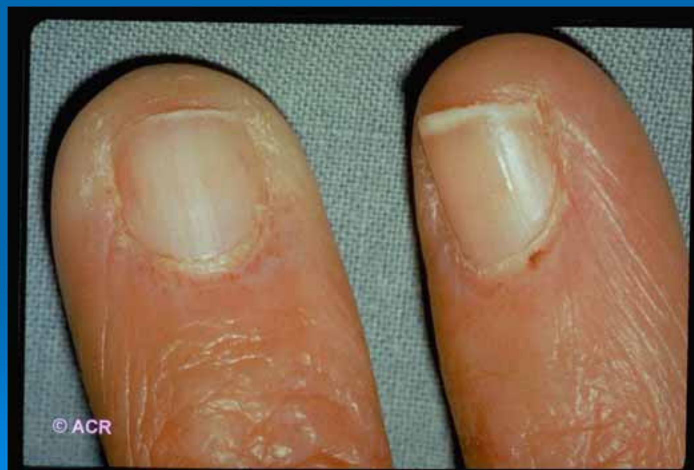
Gottron's papules - DM

PE - VASCULITIS



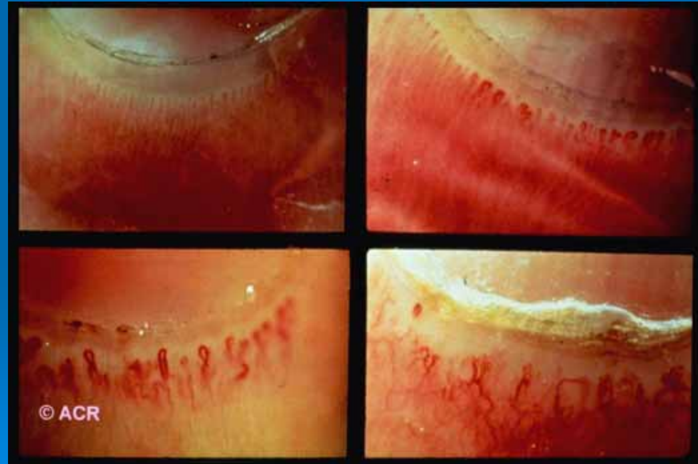


PE - PERIUNGUAL CHANGES



- SLE
- Vasculitis
- PM/DM
- MCTD

PE - PERIUNGUAL CHANGES



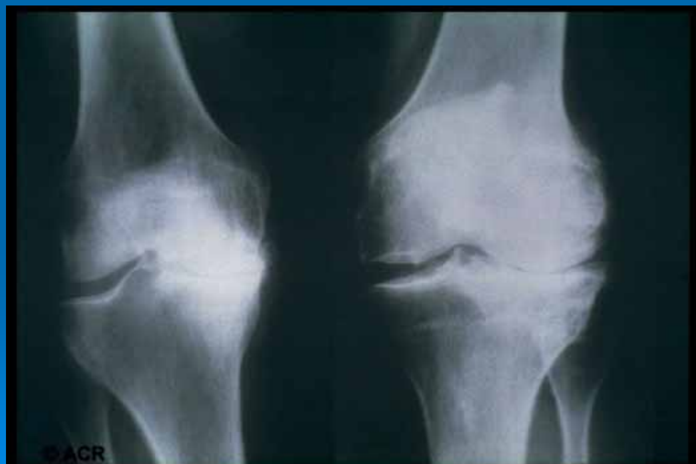
LOCATION-IMAGING

- OA
- RA / SLE
- SNSA
- CRYSTALLINE
- PERIARTICULAR

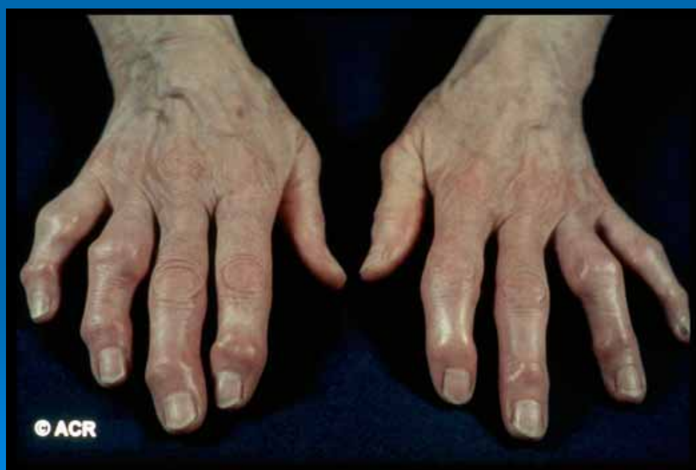
OA
C-SPINE

OSTEOARTHRITIS
HIP

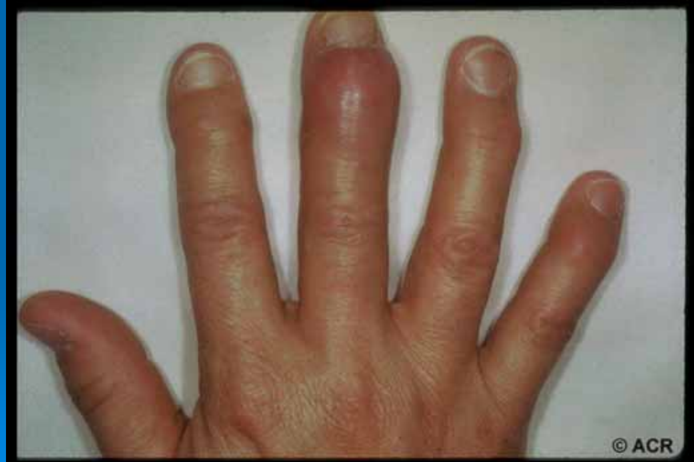
OSTEOARTHRITIS



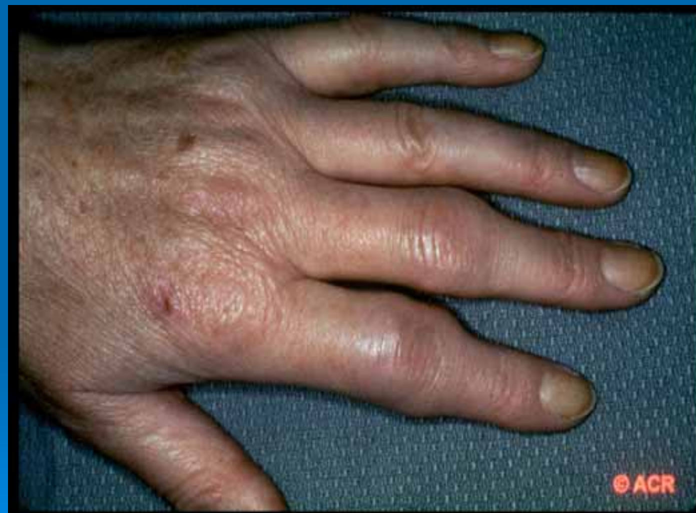
OA



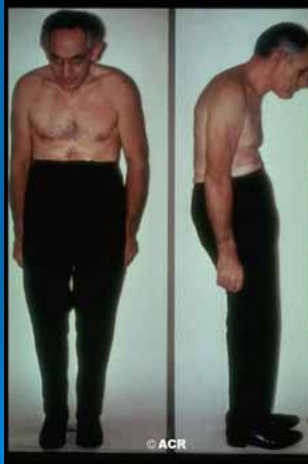
OA



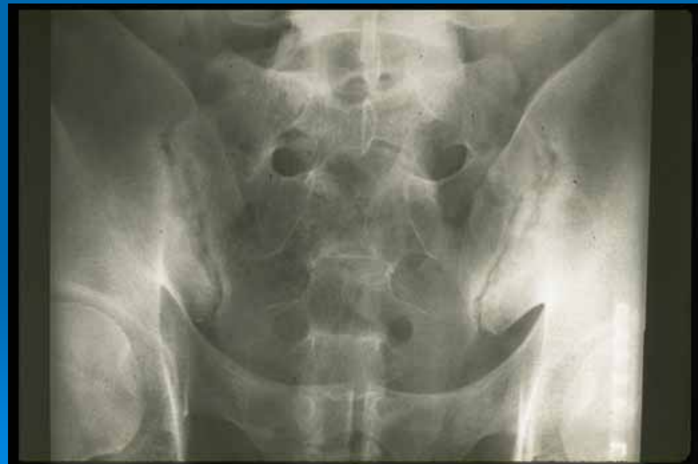
RA and LUPUS



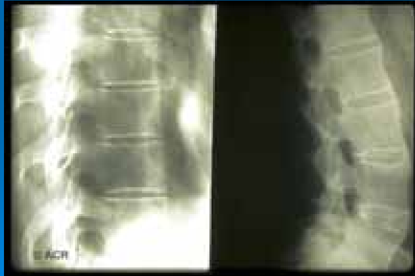
SNSA - ANKYLOSING SPONDYLITIS



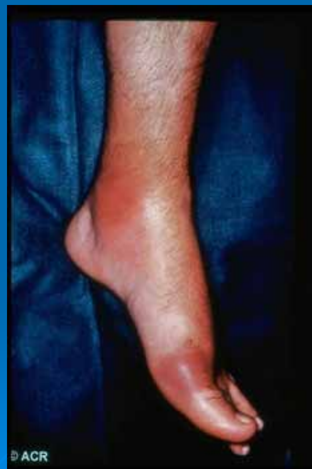
SNSA



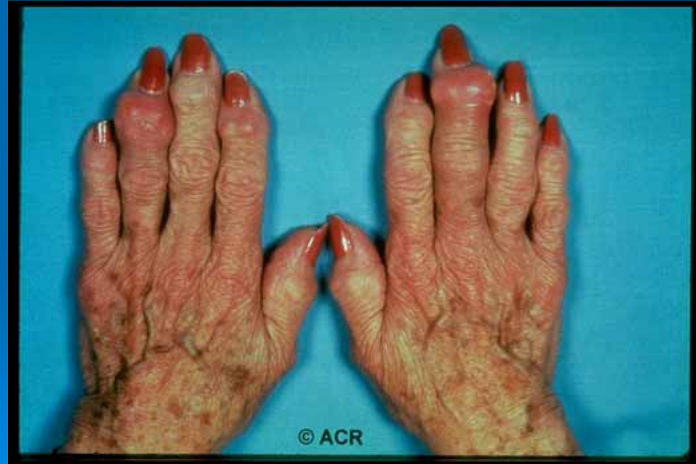
SNSA - AS



CRYSTALLINE ARTHRITIS



GOUT



LABORATORY

"…we got an ANA, ESR, and RF to check for some autoimmune disease …."

"…we got an ANA, ESR, and RF to check for some autoimmune disease…."

- It isn't that simple, and that approach really doesn't work well …
- All rheum lab tests require clinical correlation and context to interpret results …
- **Should use rheum labs to support or refute your clinical impression, not to create one …**

Pitfalls in Lab Use

- Misdiagnosis & Labeling
  - AOSD (Adult Onset Still's Disease / Systemic JIA)
    - *Is it RF (-) or RF (+) ?*
  - Pain all over with a positive ANA (+)
    - *Pain and ANA (+) is usually FMS*
  - What percentage of RA patients are RF (-) ?
    - *.5 / .7 / .8 ?*
  - What is most common cause for RF (+) in U.S. ?
- Tendency For Additional Testing
  - ENAs are often ordered following a positive ANA
    - *Runs up costs*
    - *Done needlessly to reassure no diffuse CTD*
    - *Unnecessary anxiety for the patient*

Is there some autoimmune process going on here ?

This question is best answered by a simple two step process ….

BEFORE YOU ORDER ANY LAB TEST…

1. History
2. Physical Examination

Then make an initial clinical assessment, integrating patient symptoms and signs with your knowledge of the diffuse CTDs…

BEFORE YOU ORDER ANY SEROLOGY …

- ESR and CRP
  - inflammation
- UA with micro and P:C ratio
  - glomerulonephritis
- CBC
  - anemia chronic inflammation / hemolysis / etc.
- Hep B & C serologies
  - extrahepatic manifestations of Hep B and C mimick CTDs
- TSH
  - occult hypothyroidism
- CPK
  - myositis
- CMP
  - LFTs and renal function
- Lipids
  - accelerated atherogenesis w/ inflammation
  - pseudovasculitis from cholesterol emboli syndrome

ESR

- Non-specific lab test but *very sensitive*
- Infection / malignancy / CTD / pregnancy / anemia / hypoalbuminemia / obesity/ESRD
- \- all raise the ESR
- Westergren (up to 160 mm/hr)
- Useful for "ruling out" disease:
  - GCA / PMR/RA
  - *a systemic inflammatory process*

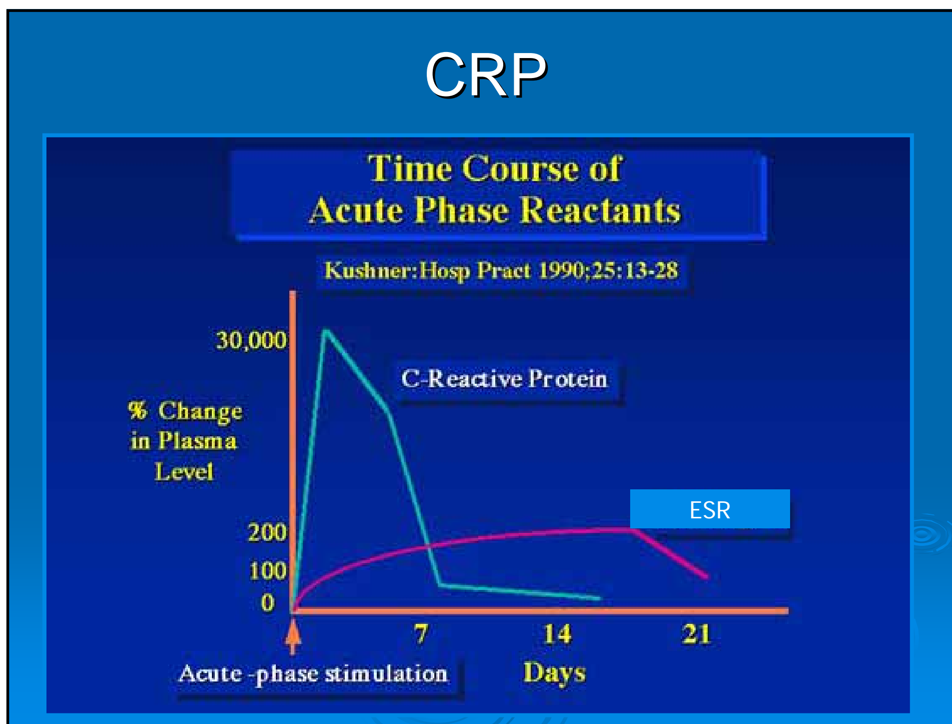
men = age/2
women = age + 10 /2

C-REACTIVE PROTEIN

- **First seen in 1930 in sera of patients with pneumococcal pneumonia**
- **A protein that could precipitate C-polysaccharide of pneumococcus**
- **Innate immune response**
- **Can activate complement**
- **Quicker rise and fall than ESR**
- **Sensitive, but not diagnostic, of any particular condition**
- **Marker for CHD (hs-CRP)**
- **Rises with BMI and CKD**

standard CRP measured as mg/dL
hs-CRP measured as mg/L

…. CRP rises with infection and ESR rises with CTD's….
(*probably not true)*



OTHER ACUTE PHASE REACTANTS

- *Alkaline phosphatase*
- *Transaminases*
- Fibrinogen
- Haptoglobin
- Serum amyloid A
- Platelet count
- Ferritin
- Albumin (decreases)
- *Total Protein*
- *Polyclonal Immunoglobulinemia (SPEP)*

SPECIFIC RHEUMATIC DISEASE LABORATORY TESTS

- RF
- CCP
- Complement
- ANA
- ENA
  - RNP
  - Sm
  - SSA & SSB
  - Scl-70 & Jo-1
- ds-DNA
- ANCA
- APLs
- Cryoglobulins
- HLA B-27
- Myositis Specific ABs

RHEUMATOID FACTOR

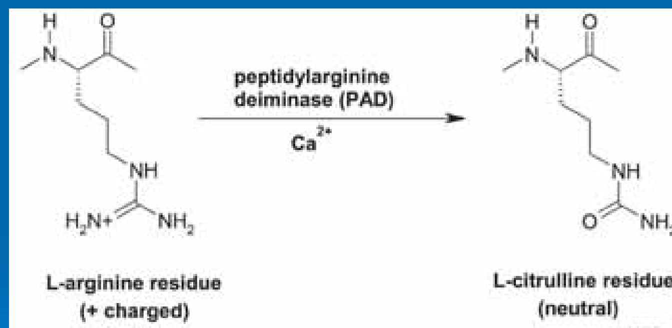
- Heterogeneous family of IgM abs directed against IgG Fc portion
- Transiently assoc with infectious diseases (TB, SBE, syphilis, HCV)
- SLE, Sjogren's, MCTD, Scleroderma, PM/DM
- IPF, cirrhosis, sarcoid
- 1-4% of healthy whites in North American
- Increase with age

- 70-80% of RA pts are seropositive for RF (with time)
- 70% of chronic HCV pts have RF
- Both types II and III cryoglobulinemia can contain RF
- Worse prognosis and more aggressive RA when RF present

Indication: Clinical suspicion for Rheumatoid Arthritis

ANTIBODIES TO CITRULLINATED PROTEINS (CCP)

Arginine residues are modified to citrulline by peptidylarginine deiminase (PAD) at sites of inflammation

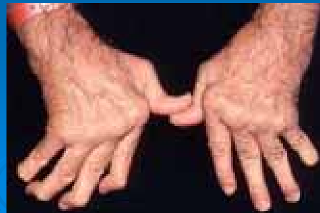


Antibodies to citrullinated proteins (CCP) are relatively specific to RA

Van Boekel et al. Arthritis and Research Therapy 2002;4:87

ANTIBODIES TO CITRULLINATED PROTEINS (CCP)

- ELISA available against CCP (cyclic citrullinated peptide)
- Very specific for RA diagnosis
- Utility in defining early and aggressive RA, *prior* to development of RF (+)
- Useful in RF positive conditions that may *mimic* RA:
  - ✓ Sjogren's
  - ✓ Chronic hepattis C
  - ✓ Cryoglobulinemia



SEROLOGIC TESTING FOR RA

- SUMMARY
- ✓ A positive RF does not mean patient has RA
- ✓ A negative RF does not mean the patient does not have RA
- ✓ CCP – a very useful test that offers similar sensitivity but superior specificity for RA
- ✓ RF is not a screening test for a diffuse CTD

COMPLEMENT

- A system of interacting serum proteins that function sequentially as initiators, regulators, and effectors of cell lysis and inflammation
- Measurement useful if: (C3, C4, CH50)
  - concern for inherited deficiency states
  - concern for immune-complex mediated disease
    - LUPUS, VASCULITIS, CYROGLOBULINEMIA, POST-STREPTOCOCCAL GN, MPGN, SBE

ANA

- ANA ***IS*** **a useful screen for <u>one particular CTD</u> -> *SLE***
  - is very sensitive - 99% - for SLE
  - is not specific for SLE
- **ANA *IS NOT* a useful screen for all diffuse connective tissue diseases**
  - not sensitive for diffuse CTD
  - not specific for diffuse CTD

Indication: Clinical suspicion for SLE, MCTD, drug-induced LE, scleroderma

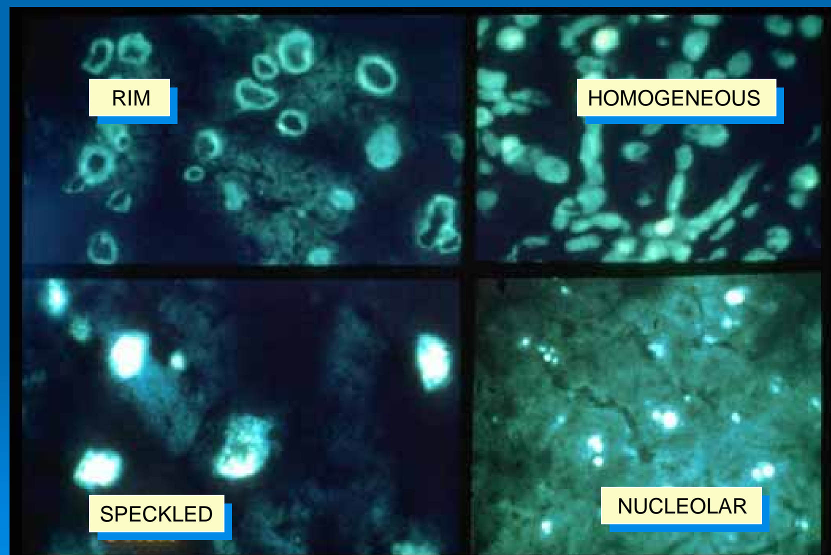
ANA

- False positives
  - 5% of healthy controls pos at 1:160 dilution
  - 10-15% of healthy controls pos at 1:80 dilution
  - 30% of healthy controls pos at 1:40 dilution
  - 1:80 AND 1:40 are normal large majority of the time
- Positive with SBE/age/liver disease/thyroid disease
- Pattern may be helpful w/ diagnosis
- Titer doesn't correlate with disease activity but does correlate with probability of underlying autoimmune dz
- Positive ANA does not, in isolation, diagnose SLE or a diffuse CTD
- Negative ANA "rules out" SLE (… most of the time)

CONDITIONS ASSOCIATED WITH A POSTIIVE ANA

- SLE
- MCTD
- Systemic Sclerosis
- Sjogren's
- RA
- PM
- DM
- Discoid lupus
- Autoimmune thyroid dz
- Autoimmune hepatitis
- PBC
- Autoimmune cholangitis
- Drug-induced lupus
- Chronic infections
- ILD
- Primary PHTN
- Lymphoproliferative d/o

ANA PATTERNS



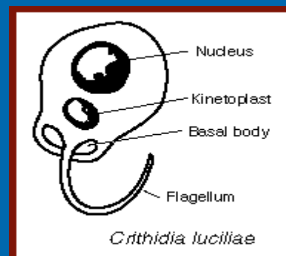
ANA PATTERNS

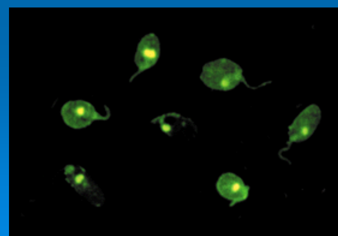
PATTERN	DISEASE ASSOCIATION
Homogeneous	Nonspecific; seen in SLE, drug-induced SLE, RA, PM-DM, vasculitis
Speckled	Nonspecific; seen in SLE, Sjogren's, PSS, PM-DM, RA – consider ordering ENA when speckled pattern noted
Nucleolar	Nonspecific; seen in PSS, PM-DM, vasculitis, SLE
Rim	Specific for SLE; occasionally seen elsewhere – consider ordering double-stranded DNA

SPECIFIC ANA's

ds-DNA

- Correlates well with renal disease activity of lupus
- Probably pathogenic
- Moderate sensitivity (70%)
- Nearly 100% specific for SLE
- Patients receiving infliximab (Remicade®), minocycline, d-PEN
- One of ACR Classification Criteria for SLE





Indications: pos ANA and clinical suspicion for SLE

EXTRACTABLE NUCLEAR ANTIGENS (ENA Panel)

RNP

- Ab to RNP - recognizes a complex of protein and small nuclear RNA designated U1
- Speckled ANA
- ELISA methodology
- Low to moderate sensitivity
- **Diagnostic of MIXED CONNECTIVE TISSUE DISEASE**
  - Presence required to make dx
  - No other ENA's should be found
  - Overlapping clinical features of SLE, PM, RA, and PSS
  - Frequently will be RF (+)
- Can be seen in ***SLE*** (30%) but usually with Sm or ds-DNA

Indication: Clinical suspicion for MCTD or SLE

EXTRACTABLE NUCLEAR ANTIGENS

Smith (Sm)

- *Ab to Sm* recognize nuclear proteins that bind to small nuclear RNAs, forming complexes involved in messenger RNA processing
- More severe disease
- Speckled ANA
- ELISA methodology
- Higher prevalence in AA & Asians with SLE
- Low to moderate sensitivity (10-40%)
- Highly ***specific*** for SLE
- One of ACR Classification Criteria for SLE

Indication: Clinical suspicion for SLE

EXTRACTABLE NUCLEAR ANTIGENS

HISTONE

- High sensitivity and low specificity
- ***Drug induced lupus*** gives anti-histone alone
- ***SLE*** gives anti-histone along with ds-DNA or Smith
- May be seen in RA
- Of limited clinical usefulness unless one suspects drug-induced lupus (INH, procainamide, hydralazine).

EXTRACTABLE NUCLEAR ANTIGENS

Ro/SS-A

- Protein-RNA complex found in both nucleus and cytoplasm
- *Sjogren's and SLE*
- 70-95% of primary Sjogren's
- 10-60% of SLE
- Found in ANA-neg lupus (if rodent tissue used to do ANA, less of an issue with Hep-2)
- Subacute cutaneous lupus (a very photosensitive lupus)
- Neonatal SLE and congenital heart block

La/SS-B

- Protein-RNA complex found in both nucleus and cytoplasm
- *Sjogren's and SLE*
- 50% of Ro/SS-A positives are also La/SS-B positive
- Unusual La/SS-B pos only
- Found in ANA-neg lupus (if rodent tissue used to do ANA, far less issue with Hep-2)
- May protect against renal disease
- Isolated La/SS-B in autoimmune hepatitis and PBC

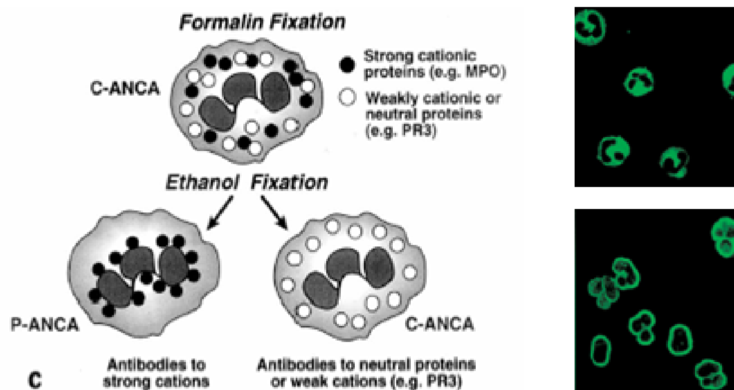
Indications: Clinical suspicion for SLE or Sjogren's

SPECIFIC NUCLEOLAR ANTIGENS

Scl-70 (Anti-topoisomerase I)	**Jo-1** (Anti-synthetase)
• Found in 20-30% of patients with diffuse systemic sclerosis • **VERY specific** • Associated with nucleolar ANA pattern • ***Lung involvement/ILD***	• Found in 30% of ***PM/DM*** patients • **HIGHLY specific** • Anti-histidyl tRNA synthetase / a cytoplasmic protein • ***Lung involvement/ILD*** • ***Fever, arthritis, Raynaud's***

Scleroderma specific antibodies: anti-RNA pol I, anti-RNA pol III, anti-U3 small nucleolar RNP, and anti-Th small nucleolar RNP – all very insensitive

ANCA
Indirect Immunofluorescence



Hoffman GS, Specks U. Arthritis Rheum. 1998 Sept;41(9):1521-37.

Anti-Neutrophil Cytoplasmic Antibody

C-ANCA

- Ab against proteinase-3 (found in neutrophils and monocytes)
- C-ANCA usually found in widespread Wegener's Granulomatosis
- C-ANCA seen less frequently with limited Wegener's Granulomatosis

P-ANCA

- Ab against myeloperoxidase or elastase
  - Several forms of systemic vascultis:
    - Churg-Strauss
    - MPA
    - SLE
- Ab against non MPO antigens
  - IBD
  - RA
  - Pauci-immune GN

ANTIPHOSPHOLIPID AB's (APLs)

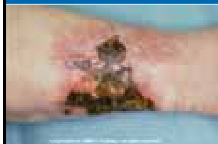
- Lupus anticoagulant (LAC)
  1. prolonged PTT or PT or final common pathway
  2. failure to correct by mixing patient plasma w/ nml plasma
  3. correction with addition of excess phospholipid or platelets
  4. ruling out other coagulopathies
- Anticardiolipin antibodies (ACLA)
  - via ELISA
- Beta-2 glycoprotein I antibodies (B2GP1)
  - via ELISA
- *All associated with venous or arterial thrombosis or recurrent fetal loss*

CRYOGLOBULINS

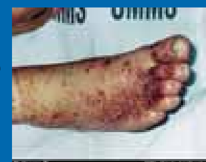
Group of serum Ig's with conformational change in the cold:

- Precipitate or gel on cold exposure
- Phenomenon reversible with re-warming
- Found in variety of clinical situations

- TYPE I
  - single monoclonal Ig or light chain
- TYPE II
  - "mixed" – a monoclonal and a polyclonal directed against the monoclonal (often RF)
- TYPE III
  - "polyclonal" – no monoclonal Ig



CRYOGLOBULINS

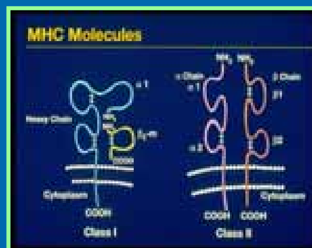


- Acrocyanosis / digital necrosis
- Palpable purpura
- Livedo reticularis
- Raynaud's
- Arthritis / GN
- Peripheral neuropathy

Type II:

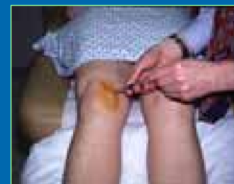
- Now recognized as being driven by chronic hep C in most cases …
- Usually low C4
- *Essential mixed cryoglobulinemia*

HLA B-27



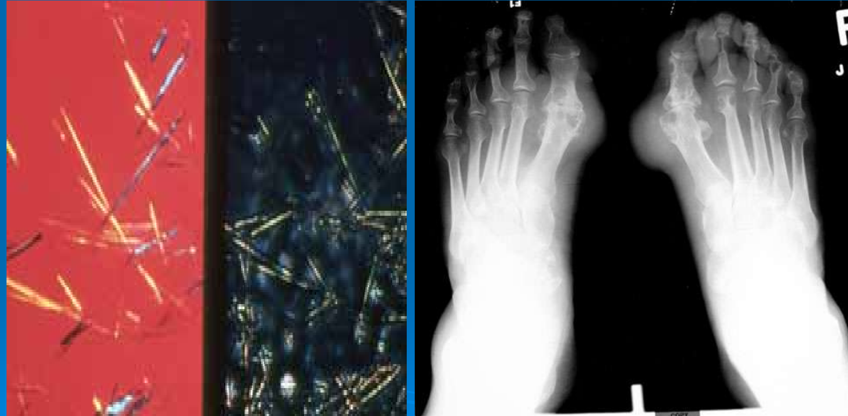
- Class I MHC cell surface marker
- Found in 7-8% of NA whites, 3-4% of NA AA's, 18-50% of Haida Indians
- Prevalence:
  - Ankylosing spondylitis – 90%
  - Reactive – 80% w/ axial disease
  - IBD-associated arthritis - 50% w/ axial disease
  - Psoriatic arthritis – 50% w/ axial disease & 15% with peripheral disease
- Do not use HLA B-27 to diagnose a SNSA

ARTHROCENTESIS

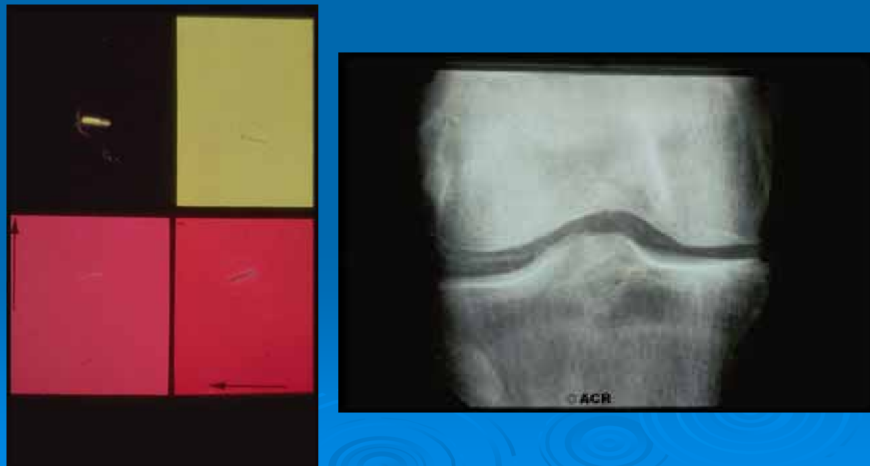


- NORMAL/NONINFLAMMATORY (0-2,000 WBC)
  - Transparent / < 25% POLYS
  - osteoarthritis / AVN / sympathetic effusion
- INFLAMMATORY (2,000-60,000 WBC)
  - Translucent / > 50% POLYS
  - RA / SLE / crystal / spondyloarthropathies
- PURULENT (50,000-100,000 WBC)
  - Infection / predominantly POLYS

GOUT



CPPD



IMAGING STUDIES

- Plain films
  - Usually not helpful for early inflammatory disease or soft tissue disease (tendinitis, bursitis)
- Bone scan
  - Can be helpful to detect subclinical inflammatory activity, not usually
- MRI
  - Very helpful for detecting spondyloarthropathy
  - Ask for specifically a sacro-iliac joint view

SUMMARY

- No lab test replaces your history, physical examination, and pattern recognition for correct diagnosis
- No lab test "screens" for autoimmune disease
- Know the general SENS and SPEC of tests for different diseases before ordering
- Say "NO" to rheum panels

BRIEF MANAGEMENT AND CLINICAL PEARLS

FIBROMYALGIA

- SUSPECT IF WIDESPREAD JOINT AND MUSCLE PAIN AND NO INFLAMMATION ON EXAM
- DON'T GO CRAZY WITH LABS
  - CBC, CHEM PANEL, TSH, ESR, CRP, ? CK
    - THAT'S IT!!!
- CAN REFER TO RHEUMATOLOGY

RHEUMATOID ARTHRITIS

- If concerned, get baseline ESR, CRP, RF, ANA, CCP
- X-rays likely not helpful early on.
- Start prednisone 10-20 mg per day if NSAIDS not helpful or contra-indicated and patient can not tolerate pain until rheumatology appointment (ideal for rheumatologist to see patient off steroids)
- There is no point to short course of steroids (pain will return).
- Refer ASAP to rheumatology

APPROACH TO ELDERLY

- PMR
- GCA
- Crystalline
- DJD

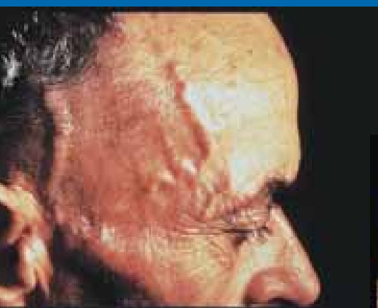
PMR

Polymyalgia Rheumatica: Characteristics (Continued)

- No Muscle Atrophy or True Weakness
- Erythrocyte Sedimentation Rate
  - >40 mm/Hr
  - In Many Patients ≥100 mm/Hr
- Rapid Relief With Small Doses of Glucocorticoids

GIANT CELL ARTERITIS

High dose steroids THEN eye exam/biopsy-call rheumatology



CRYSTALLINE ARTHROPATHY ACUTE MANAGEMENT

- Steroids
  - Intra-articular for one joint
  - Prednisone 40 mg per day for 5 days, 30 for 3, 20 for 3, 10 for 3 then stop
- NSAIDS
  - Use early
  - Avoid in CKD, CHF, PUD, chronic liver disease
- Colchicine
  - Try not to use----diarrhea
  - Avoid in CKD or very minimal dosing (one per day)
- Allopurinol or other uric acid lowering therapy
  - Does not treat acute gouty arthritis
  - However, DO NOT STOP FOR GOUT FLARE-UPS!

OSTEOARTHRITIS (DJD)

- Acetomenophen
  - 1 gram every 6 hours as needed (SAFEST)
- NSAIDS
  - REMEMBER CONTRA-INDICATIONS
  - Oral
  - New topicals
- Corticosteroid injections (not oral)
- Viscosupplementation
- Glucosamine sulfate 1500 mg qd?
- Chondroitin 1200 mg per day

QUESTIONS?