Welcome!

Extra-Articular Manifestations of RA

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INDIAN + COUNTRY ECHO

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

UCSF Health

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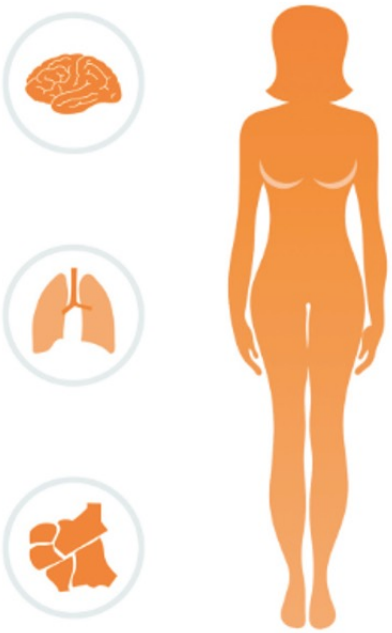
Planners Jennifer Mandal, MD, Leslie Dexheimer Gleason, RN, and Tabitha Carroway, MPH have stated they have no relationships to disclose. Speaker Wendy Grant, MD has stated she has no relationships to disclose.

Extra-Articular Manifestations of RA



NEUROLOGICAL
PERIPHERAL NEUROPATHY,
CERVICAL MYELOPATHY

PULMONARY
INTERSTITIAL LUNG DISEASE,
SEROSITIS

DERMATOLOGICAL
NODULES,
VASCULITIC RASHES

OCULAR
KERATOCONJUNCTIVITIS
SICCA, EPISCLERITIS

CARDIAC
PERICARDITIS, MYOCARDITIS,
NON-INFECTIVE ENDOCARDITIS

HAEMATOLOGICAL
NEUTROPENIA,
FELTY'S SYNDROME

Extra articular manifestations of rheumatoid arthritis

- can be seen in almost any organ system
- 0ccur in 40% of patients at some point in their disease history
- Tend to be associated with high titer serologies and more active, long-standing disease
- However, can occasionally be the presenting symptom
- Occur about equally in men and women (proportionately more common in men)

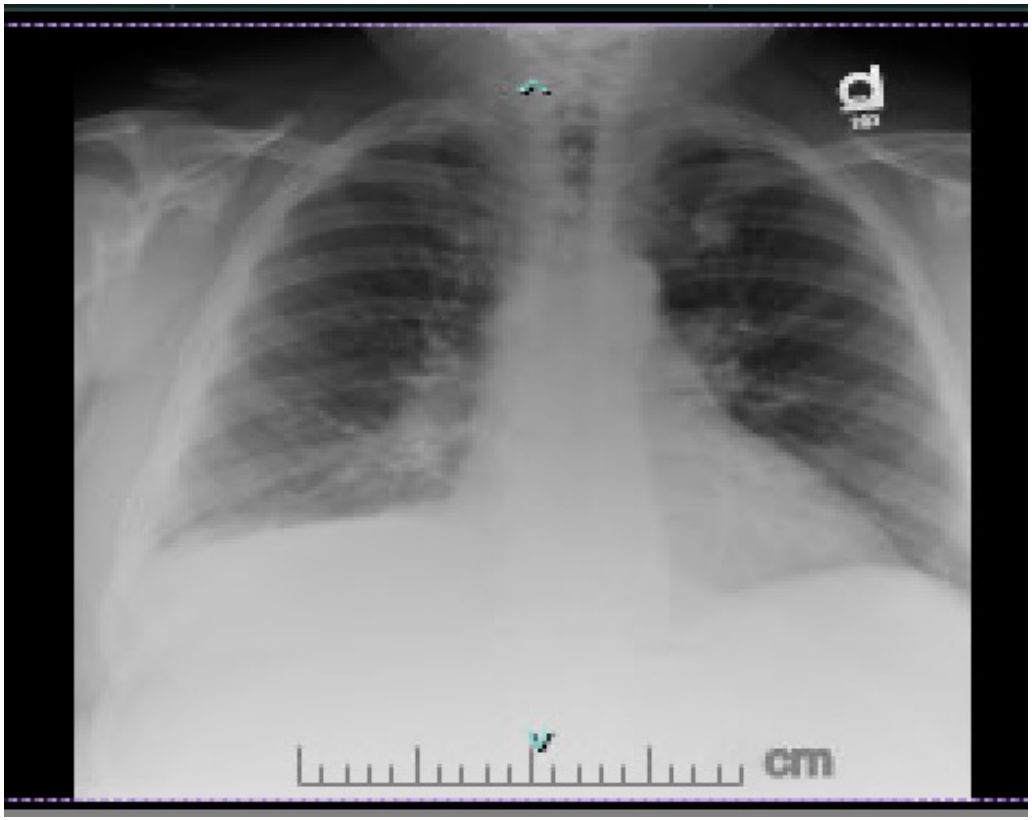
Extra articular manifestations of rheumatoid arthritis

Two broad categories:

- True disease manifestations: effects of the immunologic process on neurologic, cutaneous, ocular, pulmonary systems driven by the same cytokines that cause joint disease
- “complications” or “comorbid conditions” - drug effects, associated conditions such as anemia of chronic disease, ischemic heart disease, osteoporosis, infection
- If we include both of these categories, the average RA patient has at least one manifestation at any given time

Extra articular RA: Case #1

60 year old man with history of “gout” presents with shortness of breath



Extra articular RA: Case #1

Hospital evaluation

- CT scan: large pleural effusion; no other findings
- Thoracentesis: pleural fluid analysis
  - Glucose 50 (low); pH 7.26 (low); LDH 844 (high); total protein 3.6 (high)
- Other lab evaluation
  - CRP 167
  - RF 21
  - ANA negative
  - Discharged with ? Diagnosis but sent to rheumatology

Extra articular RA: case # 1

Outpatient evaluation

H & P: daily indomethacin for hand pain and stiffness

Exam: MCP fullness/tenderness

Additional labs: CCP ab > 250

Poll Question #1

Which of the following is true of rheumatoid pleural effusions?

a) They are transudative

b) They occur only in long-standing, poorly controlled disease

c) They are characterized by low glucose levels

d) They are more common in women

Poll Question #1

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Rheumatoid pleural effusions are more common in men; can be precede joint disease; are exudative

Glucose levels of < 60 are characteristic of RA pleural effusions

Pulmonary Manifestations of RA

Respiratory disease in rheumatoid arthritis (6 – 10%)

Interstitial

Interstitial pneumonitis/fibrosis (RA-ILD)

Usual interstitial pneumonitis (UIP)
Nonspecific interstitial pneumonitis (NSIP)
Lymphocytic interstitial pneumonitis (LIP)
Desquaminative interstitial pneumonitis (DIP)
Mixed morphology
Bronchiolitis obliterans with organizing pneumonia (Cryptogenic organizing pneumonia)
Rheumatoid nodules
Rheumatoid pneumoconiosis (Caplan's syndrome)
Apical fibrobullous disease

Pulmonary Manifestations of RA

- **Airway**
- Cricoarytenoid arthritis/central airway obstruction
- Obliterative bronchiolitis
- Bronchiectasis
- Bronchiolitis obliterans with organizing pneumonia
- Chronic small airway obstruction
- **Pleural**
- Pleuritis
- Pleural effusion
- Pleural thickening
- Chyliform effusion
- **Pulmonary vascular**
- Pulmonary hypertension
- Vasculitis

Interstitial lung disease in RA

- The most common pulmonary manifestation
- Clinically significant in about 8% of patients
- May be present but clinically silent in up to 45-60% of RA patients
- Not one single disease but a collection of radiographic patterns and severity
- ILD can occasionally pre-date joint manifestations

Interstitial lung disease in RA

- DMARDs have generally decreased the risk of extra-articular manifestations in RA, but the effect on RA-ILD is less clear
- Risk factors for ILD
  - Male sex
  - Smoking
  - More severe RA
  - High titer antibodies (RF and CCP)

Interstitial lung disease in RA

- To complicate matters, drug-induced lung toxicity is associated with many RA medications
  - Methotrexate
  - NSAIDs
  - Leflunomide
  - Anti TNF agents
  - Rituximab
  - Tocilizumab

Interstitial lung disease in RA

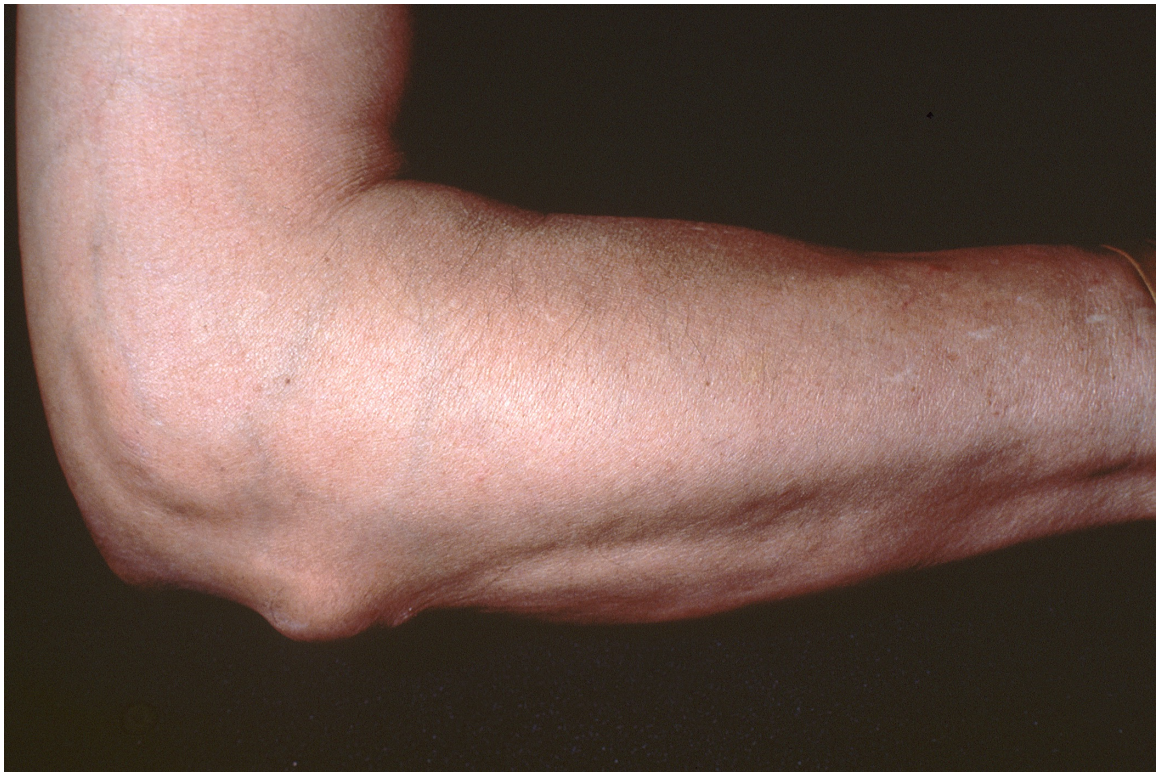
- Low threshold to evaluate pulmonary symptoms in an RA patient (cough, dyspnea, new crackles on lung exam)
- Evaluation:
  - PFTs
  - High resolution CT scan
  - Consultation with pulmonary

Poll Question #2

Which of the following statements about rheumatoid nodules is incorrect?

a. They occur more frequently in smokers
b. They occur almost exclusively in patients with positive serologies (RF, CCP)
c. They can be found in the lungs and myocardium
d. They are always seen in conjunction with severe active joint disease

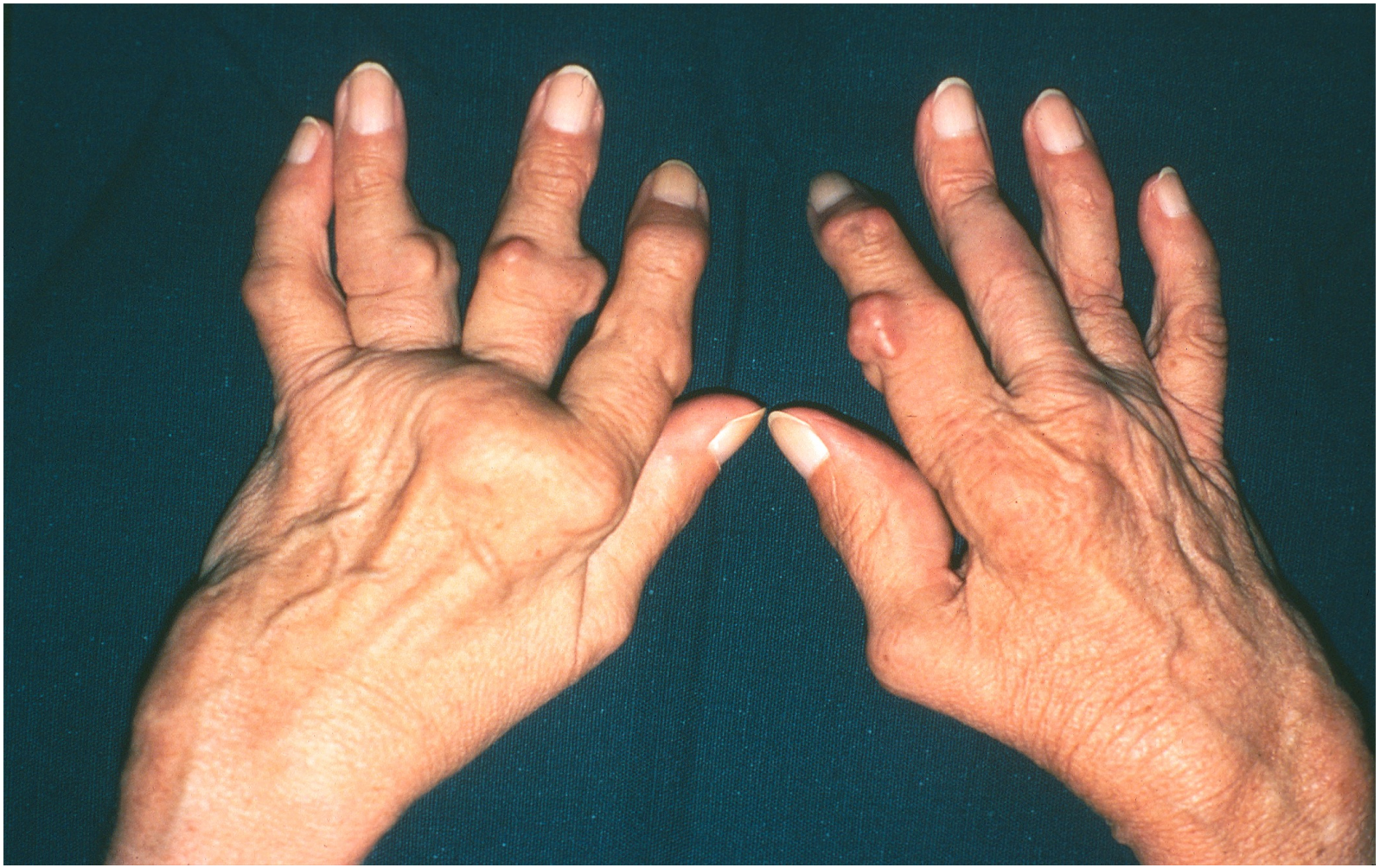
Rheumatoid nodules



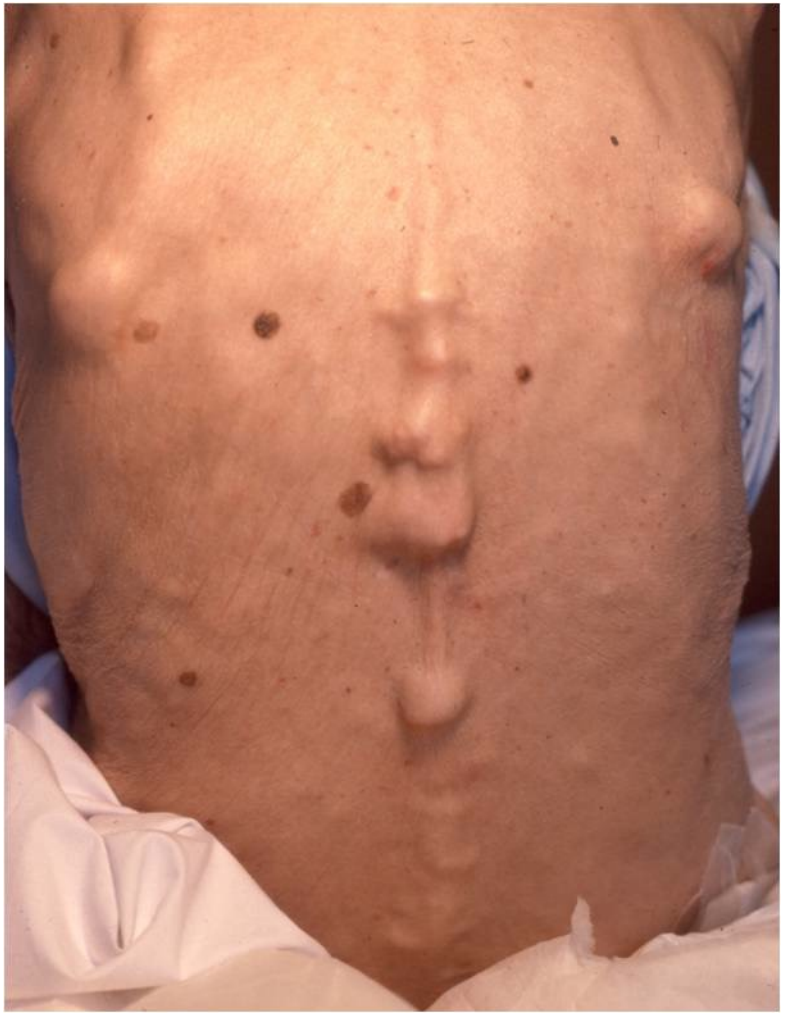
Rheumatoid nodules

- Nodules occur in about 30% of RA patients at some point in their disease history
- Associated with tobacco use, positive serologies (RF, CCP)
- Higher incidence in males > females
- Occur at areas of pressure
- Also can be seen in the lungs and heart (myocardium, valves - rare)
- “Rheumatoid nodulosis” refers to the presence of rheumatoid nodules in the absence of significant synovitis
- Pathology: focal central fibrinoid necrosis with surrounding fibroblasts

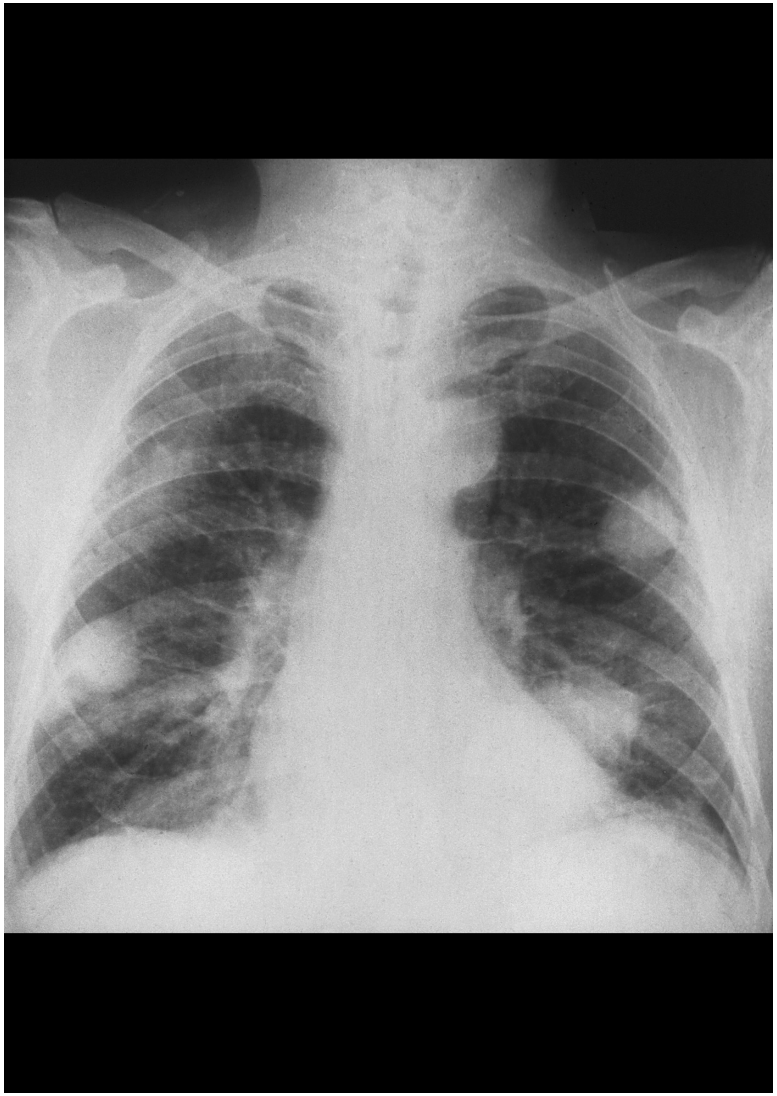
Rheumatoid nodules



Rheumatoid nodules



Rheumatoid nodules



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“Rheumatoid nodulosis" can occur in quiescent joint disease; sometimes seen in association with methotrexate use

Extra articular RA: Case #2

- 39 year old woman with RA for 20 years
- poorly controlled on adalimumab, methotrexate, 10-15 mg prednisone
- Prior treatments with gold, hydroxychloroquine, sulfasalazine, other TNF inhibitors

Extra articular RA: Case #2

CBC over a two-year period

- WBC 5.3 → 2.45 -> 1.0
- % neutrophils 49 → 4.0 → 0

Poll Question #3

Which of the following is NOT a hematologic complication of rheumatoid arthritis?

a) Anemia of chronic disease
b) Hemolytic anemia
c) Thrombocytosis
d) Large granular lymphocytosis
e) Medication-induced cytopenias

Hematologic manifestations of RA

- Causes of **neutropenia** in an RA patient
  - Felty Syndrome: neutropenia, splenomegaly, lower extremity ulcers
    - RF +/CCP+
    - long-standing severe RA
  - Large granular lymphocytic leukemia
  - Medication effect (MTX, leflunomide, SSZ, TNF inhibitors, IL-6 inhibitors, JAK inhibitors)

Hematologic manifestations of RA

Common

Anemia

- Medication: methotrexate, azathioprine, leflunomide, SSZ, NSAIDs
- Anemia of chronic disease: mild, normocytic, very common
- Iron, B12 and folate deficiency are also more common in RA

Hematologic manifestations of RA

Rare

Non Hodgkin Lymphoma: 2 fold increased risk in RA

Felty syndrome

- Associated with severe seropositive RA, splenomegaly, other extra-articular manifestations (vasculitis), recurrent infection

Large granular lymphocytic leukemia

- Can occur early in RA
- Indolent course

Hematologic manifestations of RA

- Bone marrow biopsy → large granular lymphocytosis (polyclonal)
- Resolved with optimal treatment of RA

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d) Large granular lymphocytosis
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Hemolysis is not a typical feature of RA

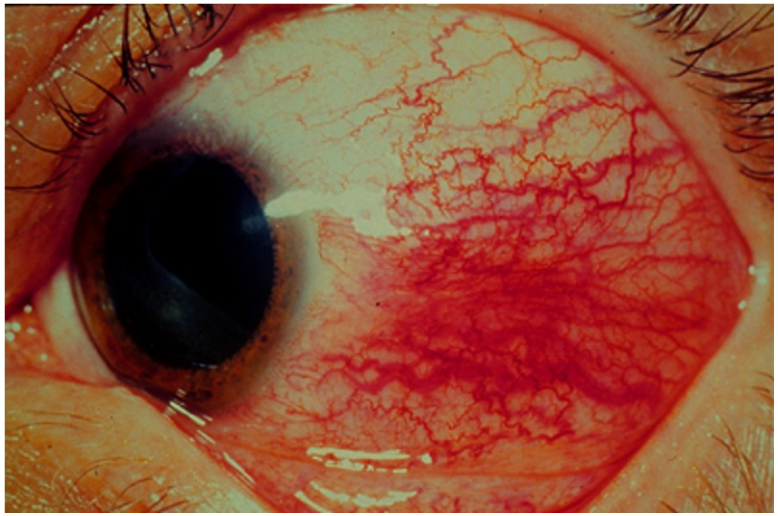
Ocular disease in RA

- 18% incidence in RA
- **Corneal disease (most common)**
  - Dry eye (KCS)
  - Sjogren's with positive SSA/SSB (high incidence of RA/Sjogren's overlap in Navajo population)

Ocular disease in RA

- **Scleral disease**

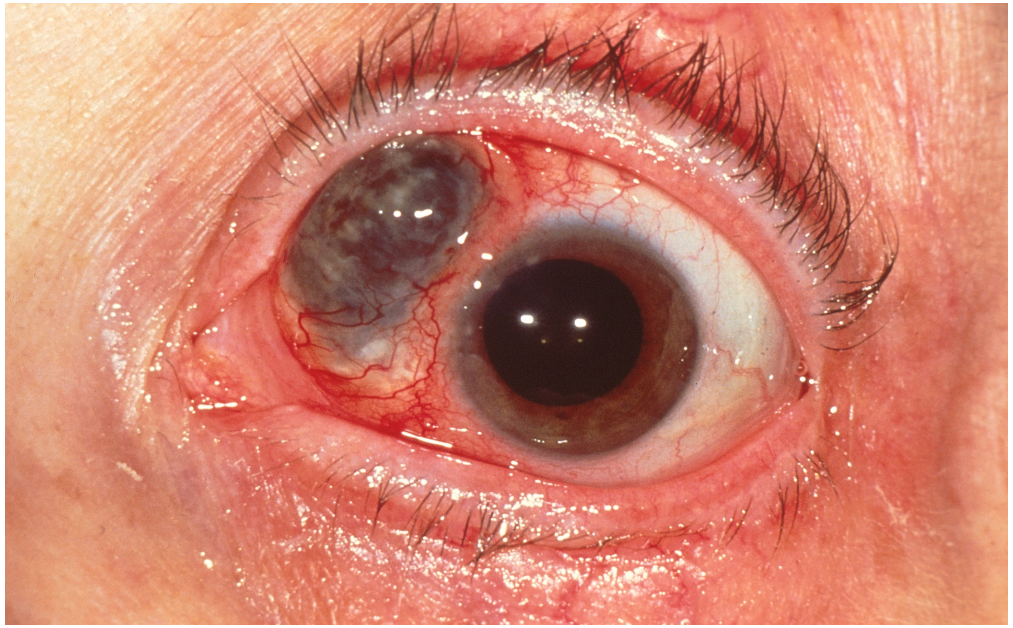
  Episcleritis: usually acute in onset; discomfort rather than pain; usually benign and self-limited



Ocular disease in RA

- **Scleral disease**

  Scleritis: severe pain; usually requires systemic therapy; potential for severe complications, including scerlomalacia perforans



Other extra articular manifestations of RA

Cardiovascular

- Estimated risk of CV disease is 50% higher in RA patients

- **Contributing factors**
- Chronic inflammation ---> increased atherosclerosis
- Metabolic syndrome is more common in RA
- Use of steroids and NSAIDs
- Inactivity secondary to physical limitations

Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies.Aviña-Zubieta. ArthritisRheum. 2008;59(12):1690.

Other extra articular manifestations of RA

Skin: pyoderma gangrenosum; ulcers due to vasculitis

GI: tend to be secondary to medication

rare incidence of vasculitis

Renal: very rare to see glomerular disease, interstitial disease. In long-standing RA, secondary AA amyloid can cause proteinuria and renal insufficiency

Metabolic: increased risk of osteoporosis and metabolic syndrome

Psychiatric: increased incidence of depression/chronic pain

Neurologic: mononeuritis multiplex (really a vasculitic process)

Extra articular manifestations of RA

- Nodules are most common (30%)
- Ocular complications are common (18%)
- Pulmonary complications occur in 8-9 %, with ILD being most the most common; up to 60% with subclinical disease
- Some combination of disease-specific manifestations and comorbid conditions occur in most patients
- Treatment of RA almost always involves addressing more than the joints

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