Sarcoidosis: Diagnosis, Detection, and Management

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Objectives

- Overview: epidemiology, clinical presentation
- Diagnostic criteria based on ATS guidelines
- Screening/detection of extrapulmonary sarcoidosis
- Treatment of sarcoidosis

Epidemiology – adults

- Globally, high prevalence noted in Swedish/Dutch populations
- In the US, incidence & prevalence is highest among African Americans, lowest in Asian and Hispanic Americans
    - ~4 fold higher prevalence among AA compared to Whites
    - AA women have the highest mortality (2-4 times higher)
- Prevalence similar among men and women
- Women have later onset of disease
- Higher risk in twins and in 1st degree relatives

Pathogenesis and natural course

Familial
Blau syndrome

Polygenic
DRB1: Lofgren's
BTNL-2: Germans

Race

Genetic predisposition

Antigen

Berrylium

Post 9/11

Infection
TB, histo, P. acnes

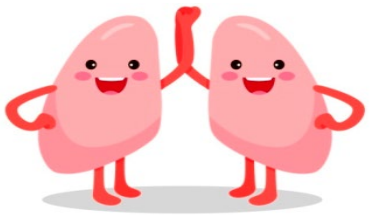
Th1
(IFN, TNF)

Granuloma

2/3

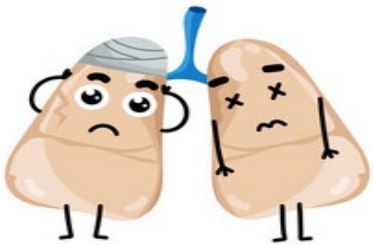
1/3

Th2
(IL4, 7,13
STAT6
MMP12
MRP14)



Resolution

Chronic sarcoidosis & fibrosis

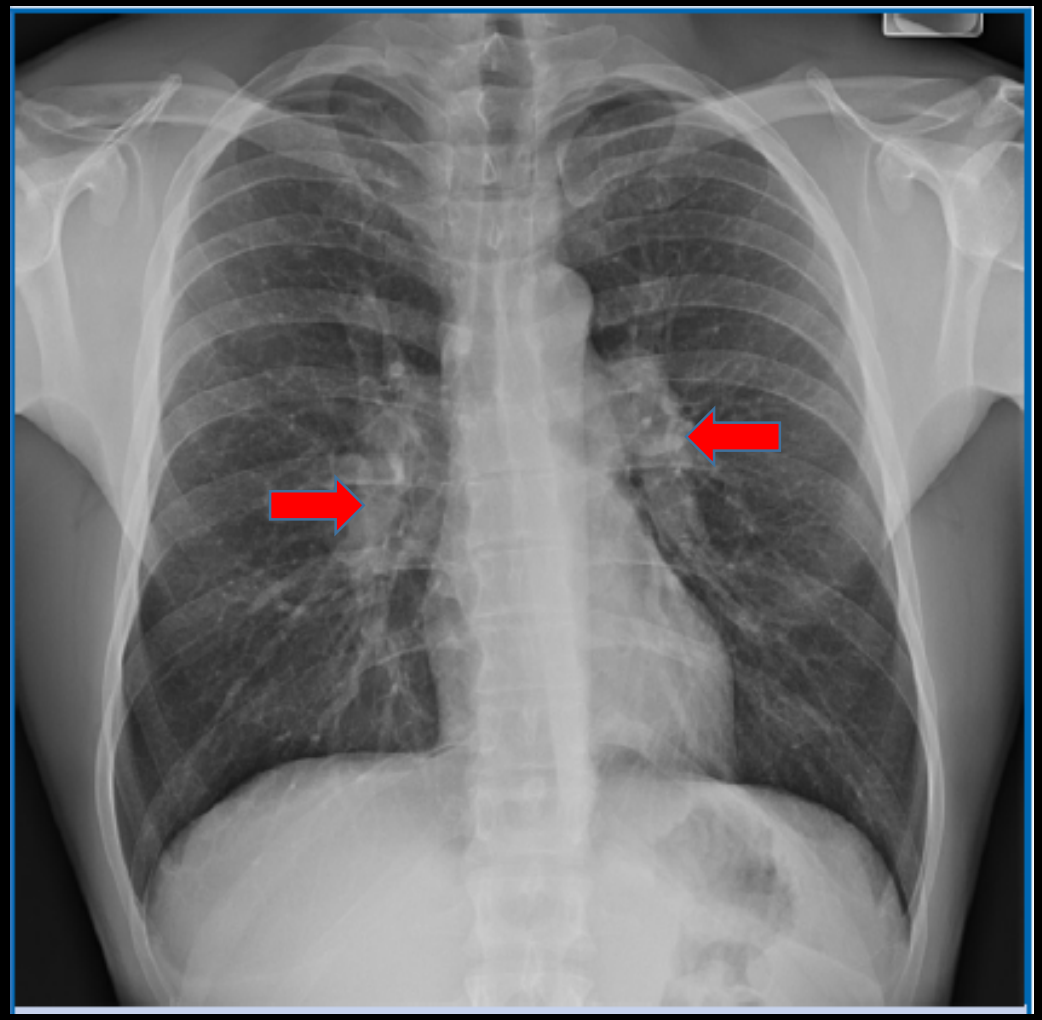


Clinical Presentation

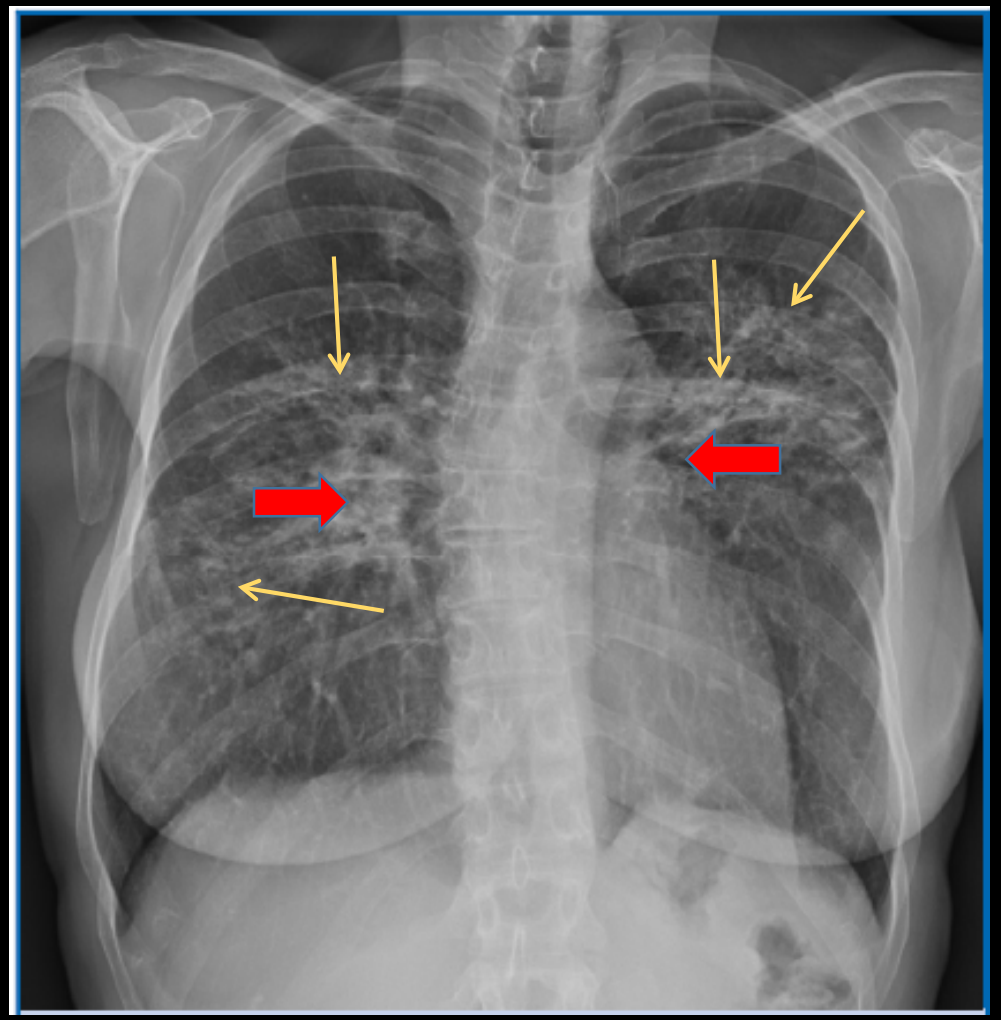
- Up to 50% are asymptomatic with incidental hilar adenopathy seen on CXR
- Symptoms depend on the organs involved
- Common respiratory symptoms:
    - Cough, dyspnea, chest pain
- On pulmonary physical exam,
    - Wheezing may be present; crackles and clubbing are rare
    - The lung exam is often normal despite radiographic abnormalities

Chest Imaging:

Stage 1 disease: bilateral hilar adenopathy without evidence of parenchymal lung involvement

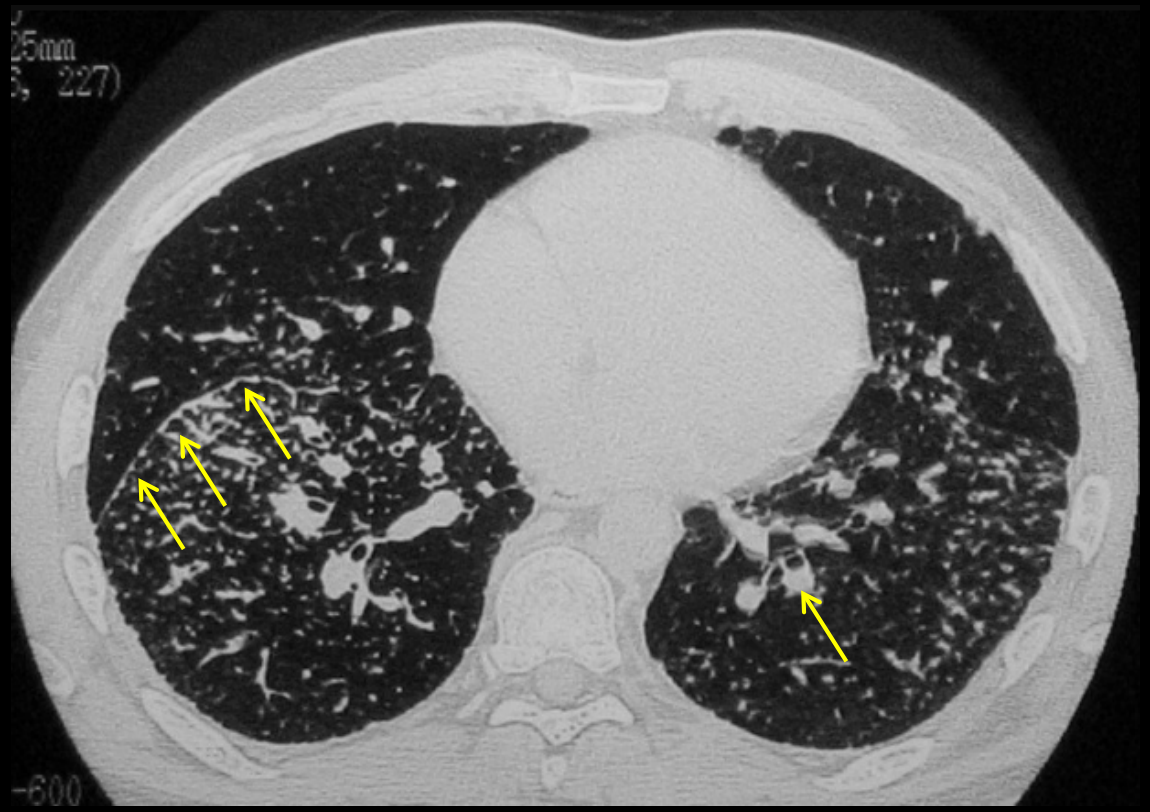


Stage 2 disease: bilateral nodular parenchymal opacities in a perihilar and mid-lung distribution associated with bilateral hilar adenopathy

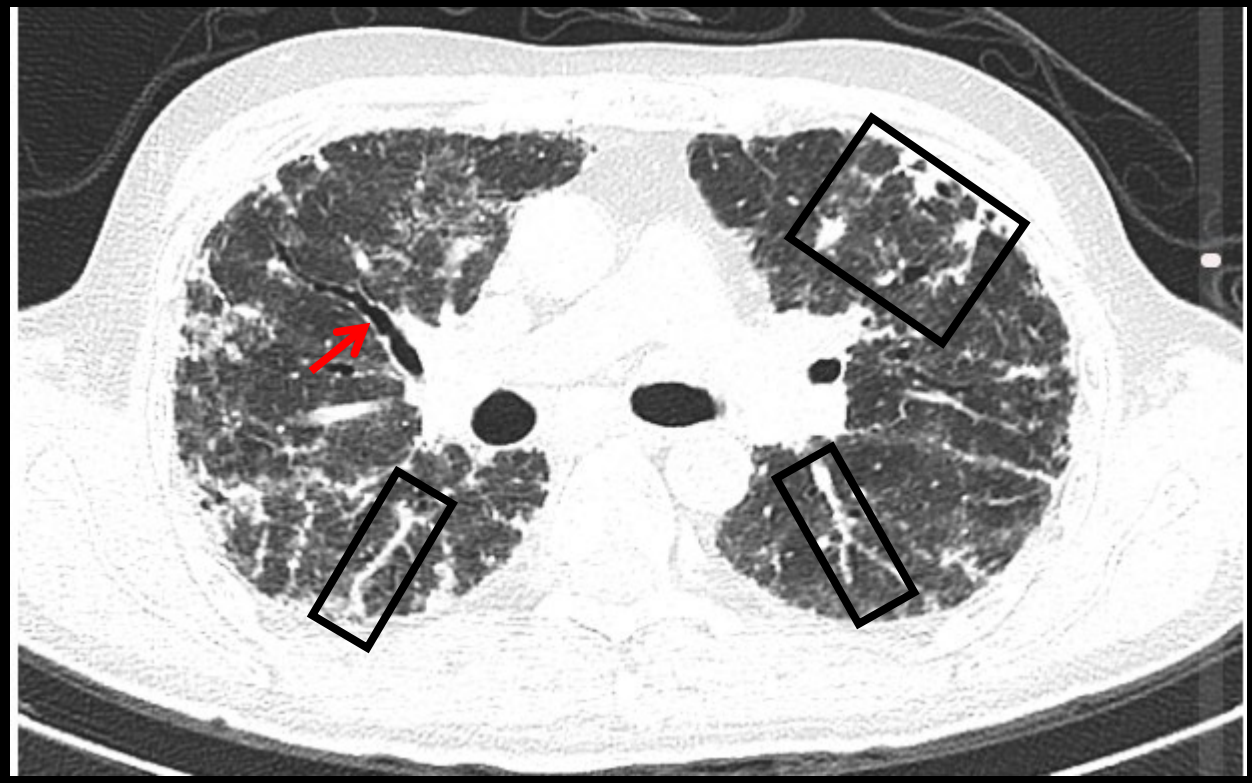


Chest Imaging:

Stage 3 disease: small pulmonary nodules that are upper-lobe predominant and perilymphatic in Distribution. No adenopathy



Stage 4 disease: parenchymal scarring, traction bronchiectasis, cysts

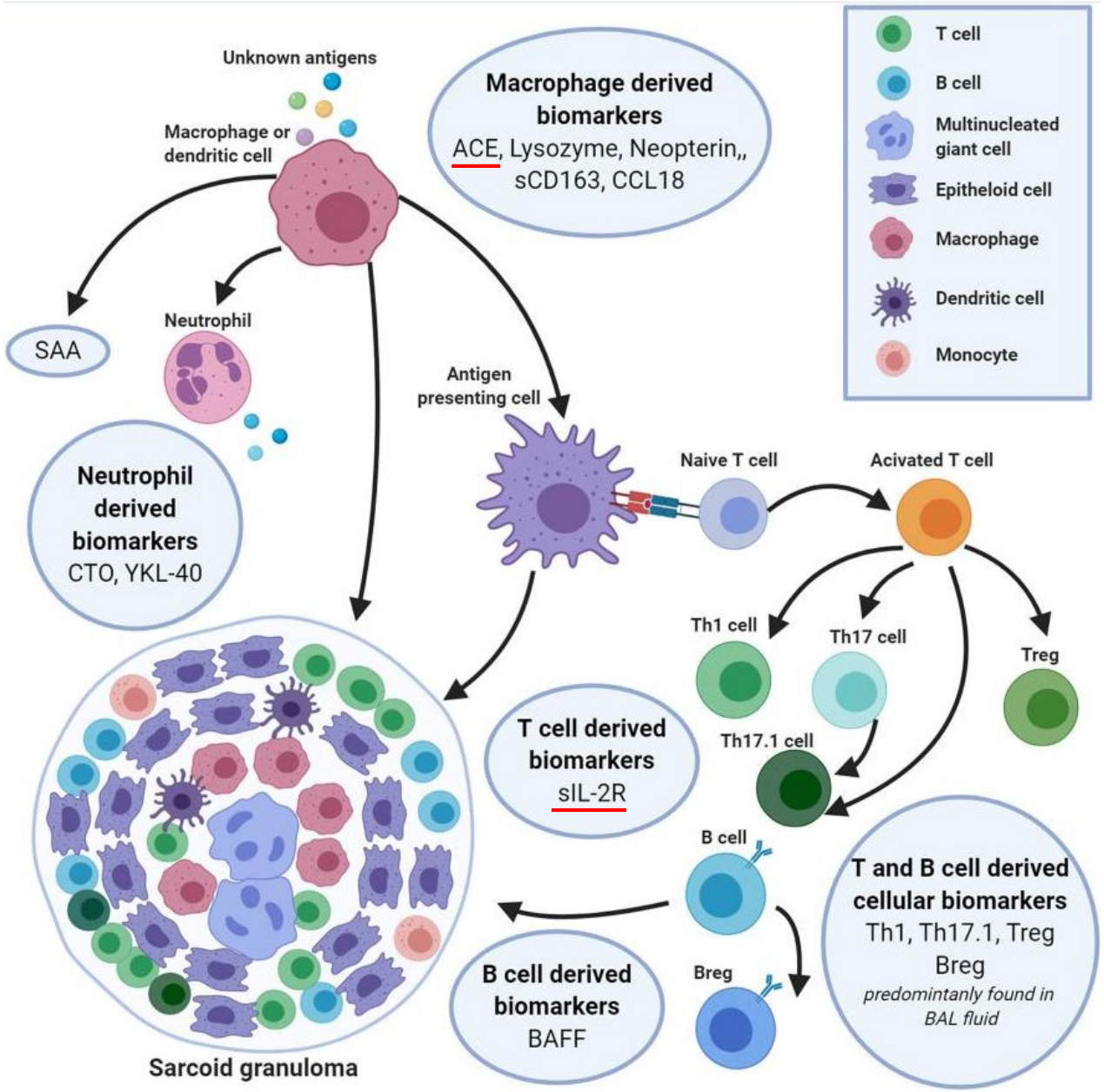


Diagnostic Criteria

Three major criteria:

1. A compatible clinical presentation
2. Non-necrotizing granuloma on biopsy
3. Exclusion of alternative causes of granulomatous disease

Role of biomarkers



Role of biomarkers

- Angiotensin converting enzyme:
  - Can be checked in serum and the CSF
  - Sensitivity: 22 – 86%
  - Specificity: 54 – 95%
  - Can be elevated in TB, berylliosis, histoplasmosis, Gaucher's disease

- Soluble Interleukin 2 (IL-2):
  - Serum and CSF (less readily available)
  - Can be used to monitor disease progression
  - Pts w/ confirmed sarcoidosis and high IL-2 level tend to respond well to anti TNF therapy
  - Lacks specificity: can be elevated in other granulomatous disease, malignancy, autoimmune diseases

How to biopsy mediastinal nodes?

- Endobronchial Ultrasounds guided Fine Needle Aspiration (EBUS-FNA) is the diagnostic modality of choice
  - Outpatient procedure w/ general anesthesia or moderate sedation

- Mediastinoscopy is the alternative
  - More invasive, expensive, longer hospital stay without a much higher diagnostic yield

Table 2. Key Infectious and Noninfectious Differential Diagnoses for Granulomatous Lesions

Infectious	Non Infectious
Bacteria	Malignancy
Tuberculosis	Lymphoma
Nontuberculous mycobacteria	Sarcoid like reaction to tumor
Aspiration pneumonia	Lymphoid granulomatosis
Brucella	Germ cell tumor
Trophorema whippelii	
Francicella tularensis	Autoimmune or immune dysfunction
Bartonella hanselae	ANCA-associated vasculitides (GPA, MPA, and EGPA)
Fungi	GLILD associated with CVID
Aspergillus	Rheumatoid nodules
Histoplasma	Langarhans cell histiocytosis
Blastomyces	IgG-4-related disease
Coccidioides	Inflammatory bowel disease
Cryptococcus	Primary biliary cholangitis
Pneumocystis	Autoimmune hepatitis
Viruses	Exposures
Herpes zoster	Hypersensitivity pneumonitis
	Hot tub lung syndrome (MAC exposure with hypersensitivity features)
Parasitic	Pneumoconiosis (such as beryllium, titanium, aluminum, zirconium, cobalt, and others)
Toxoplasma gondi	Drug-induced granulomatous disease (including but not limited to IFN, checkpoint inhibitor, anti-TNF, and/or biologic therapies)
Schistosomiasis	Foreign body granulomatosis (such as talc aspirated or injected, tattoo ink)
Leishmaniasis	Steatosis (lipogranulomas)
Echinococcosis	Idiopathic
Enterobius	Sarcoidosis
Dirofilaria	Necrotizing sarcoid granulomatosis
	Histiocytic necrotizing lymphadenitis (Kikuchi's disease)
	Granulomatous lesions of unknown significance syndrome
	Bronchocentric granulomatosis

Questions?

Lofgren Syndrome

- Acute form of sarcoidosis
- Presence of erythema nodosum, migratory polyarthralgia, bilateral hilar lymphadenopathy and fever highly specific (>90%) for sarcoidosis
- Prognosis is excellent

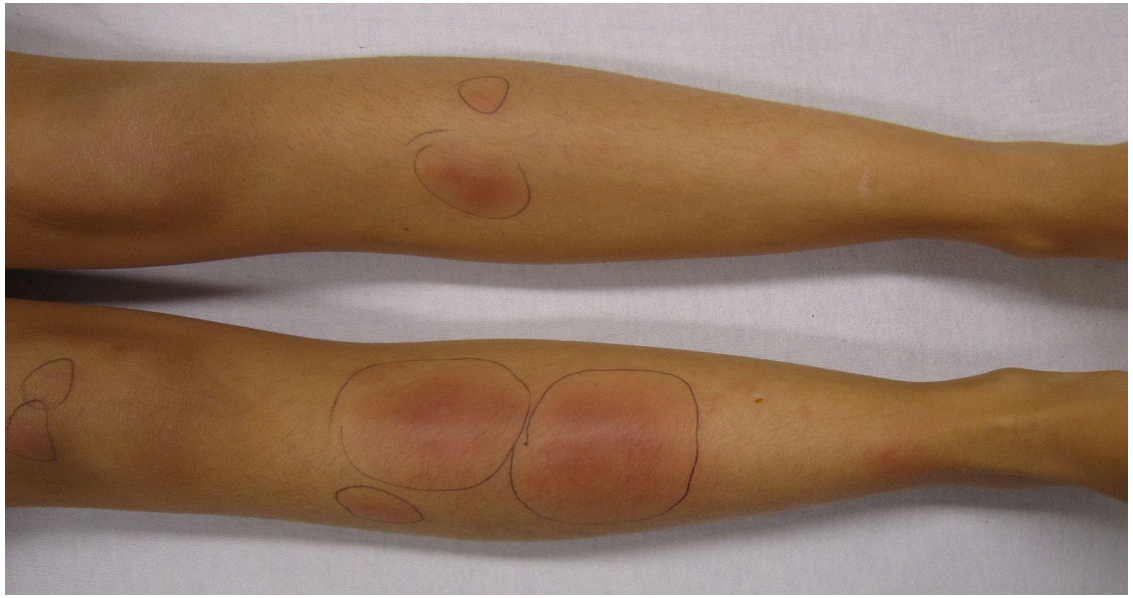


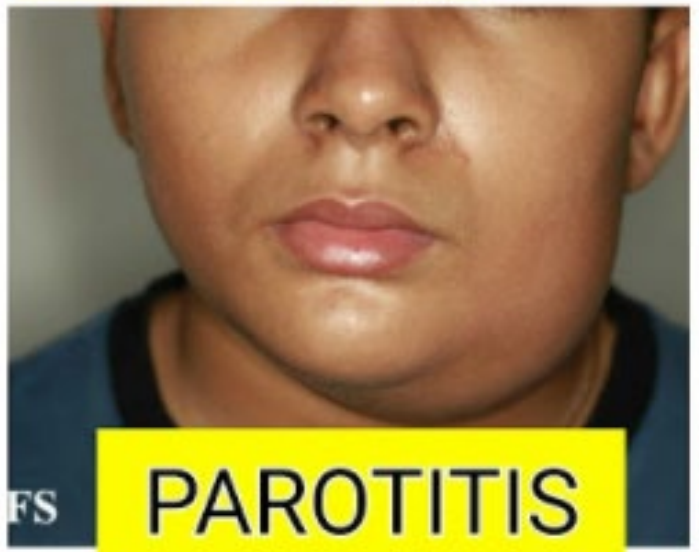
Image: wikipedia.org

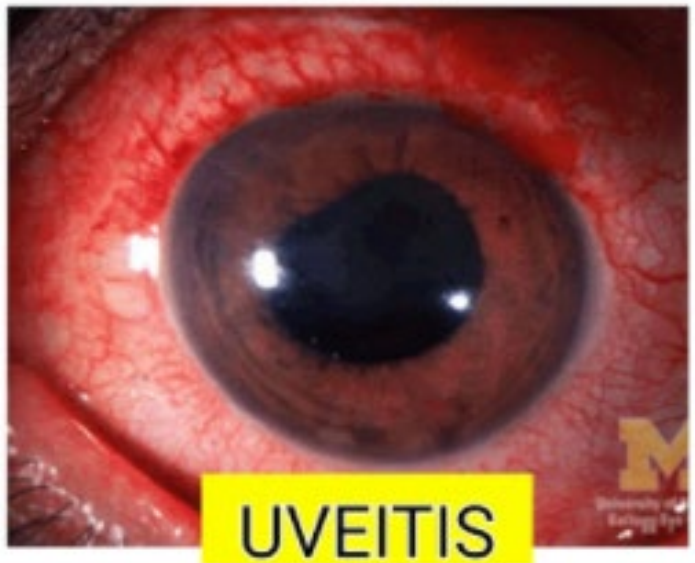
Erythema Nodosum

Heerdfordt Syndrome

- Triad of:
  - Parotid gland enlargement
  - Facial nerve palsy
  - Uveitis

- Highly specific for sarcoidosis
- Most pts have thoracic involvement





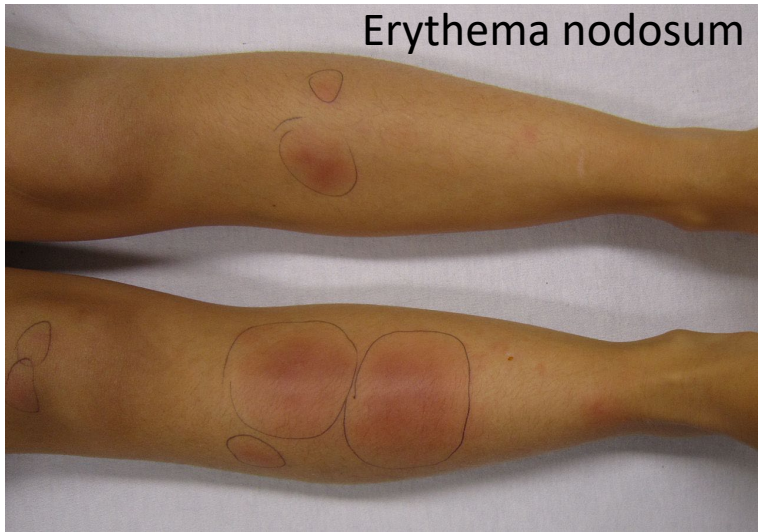
So we’ve established a diagnosis of pulmonary sarcoidosis. Now what?

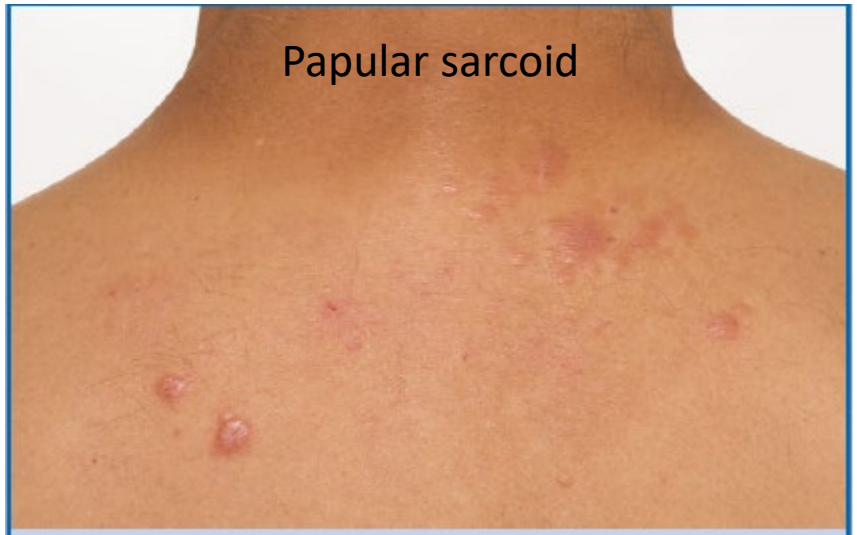
Detection of Extra-thoracic Disease

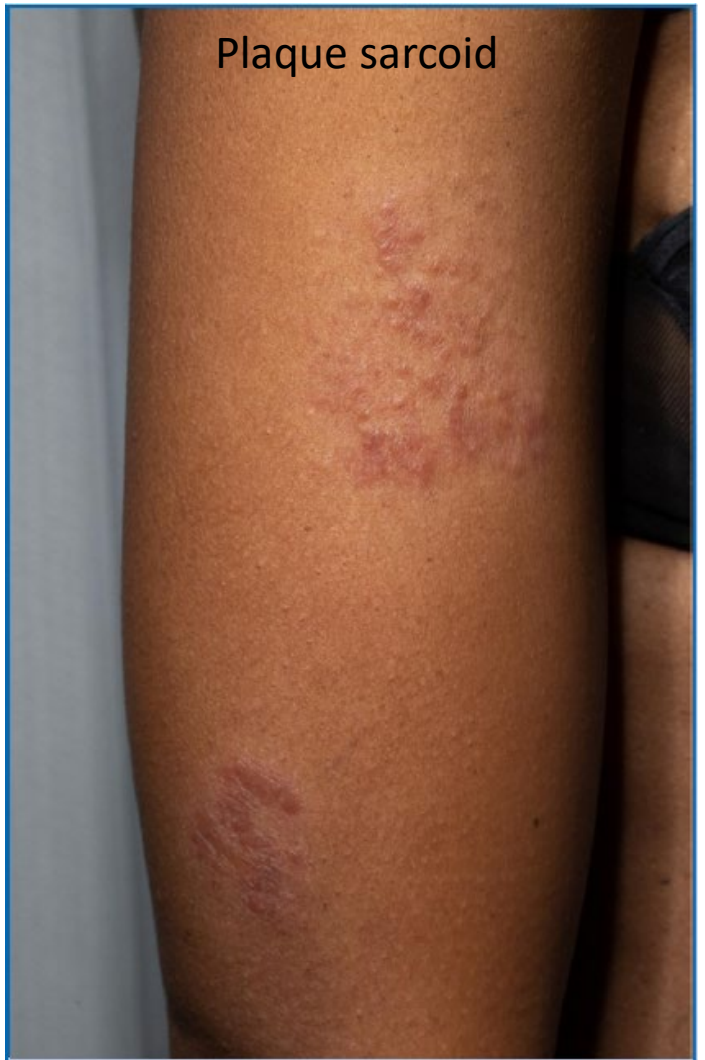
- Extra-thoracic involvement occurs in >50% of cases
- <3% present exclusively with extra-thoracic disease
- Asymptomatic extra-thoracic involvement is common, and requires additional screening tests

Cutaneous sarcoid

- Most common extrapulmonary manifestation
- Don’t biopsy erythema nodosum
- Most patients have remission within 2 years
- Treatment:
  - 1st line: topical ultrapotent steroids (clobetasol, halobetasol)
  - 2nd line: hydroxychloroquine or oral steroids
  - 3rd line: MTX
  - NSAIDs for erythema nodosum

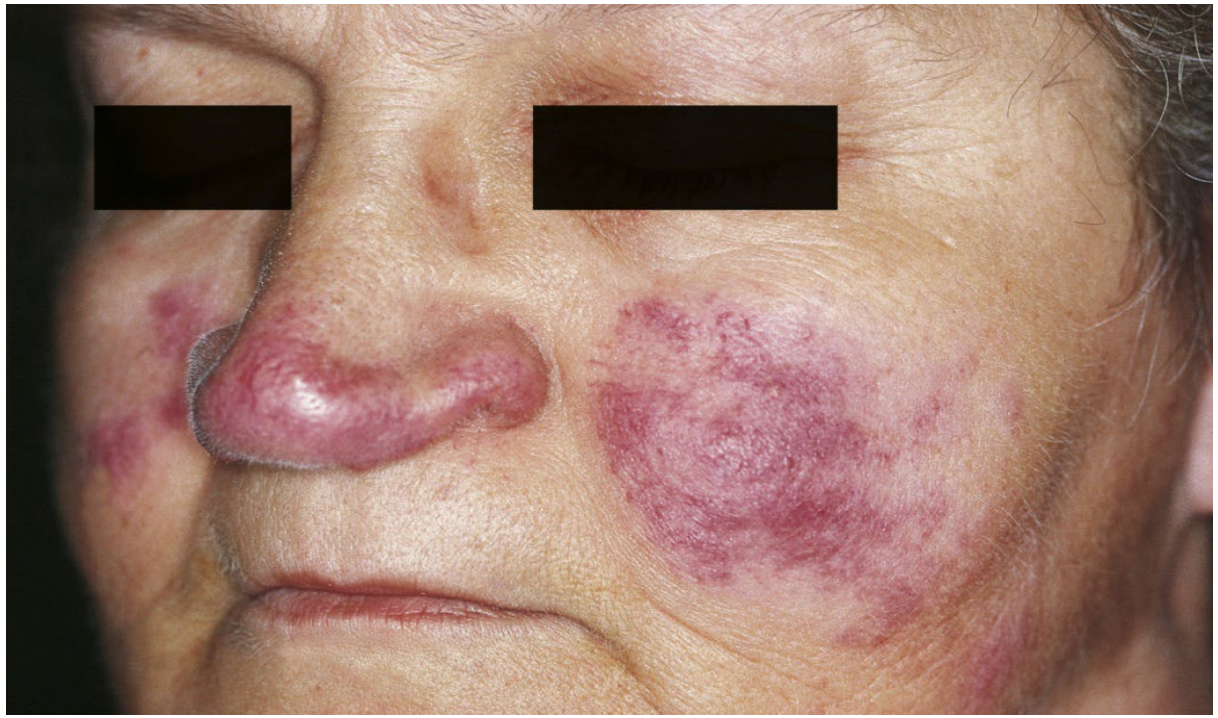




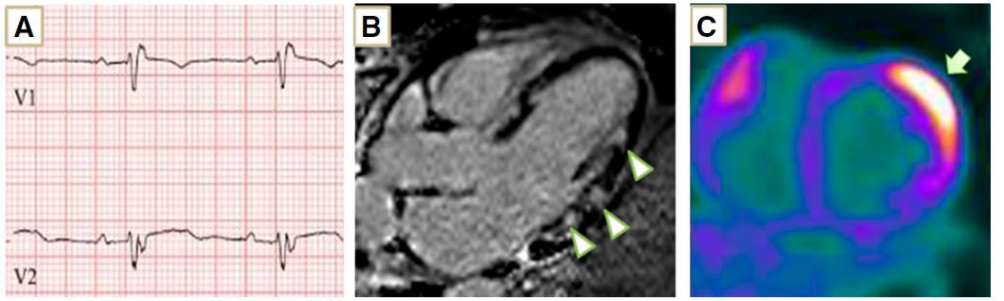


Cutaneous sarcoid - Lupus Pernio

- Violacious skin plaques with predilection for nose, cheeks, ear and fingers
- Concurrent intrathoracic involvement common
- Biopsy of the affected skin would show granuloma



Cardiac sarcoidosis

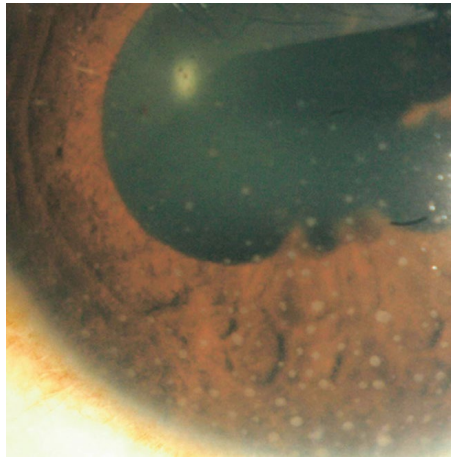


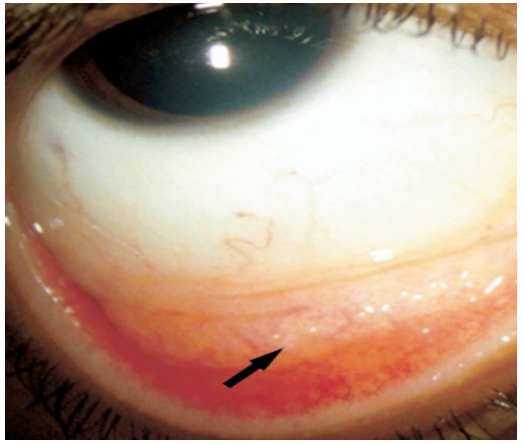
- ~25% prevalence on autopsy
- Second leading cause of death behind pulmonary sarcoidosis
- 5% are symptomatic
  - Palpitations, chest pain, dizziness, syncope, sudden death
- Common issues:
  - Heart block (complete or bundle branch)
    - ~1/3 of all cases of adult onset complete heart block
  - Ventricular arrhythmias (with clear coronaries)
  - Atrial arrhythmias (uncommon)
  - Heart failure (myocarditis)

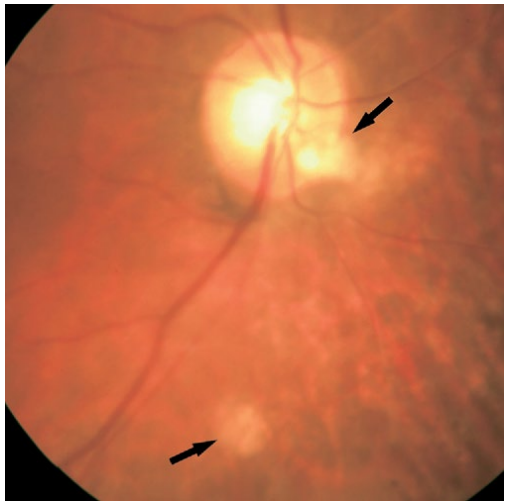
Cardiac sarcoidosis

- No optimal screening test
- Screening: Baseline EKG at time of diagnosis for asymptomatic sarcoidosis
- Cardiac MRI w/ contrast best for detection if cardiac involvement is suspected (abnormal EKG or smx)
  - Buzz words:
    - "Late gadolinium enhancement"
- TTE can be used to follow response to therapy if diagnosis of sarcoid cardiomyopathy already established
- Myocardial biopsy has poor yield (~13%)
- Treatment or at least close follow up are necessary
  - Non life threatening disease: prednisone 40-60mg/day. Slow taper. Most experts recommend at least 1-2 years of prednisone. MTX, infliximab 2nd and 3rd agent respectively. If high risk of steroid toxicity (obese, diabetes, etc, start pred + MTX)
  - Life threatening myocarditis or VT storm: initially solumedrol (1mg/kg upto 1g/day) followed by taper as above

Ocular Sarcoidosis:





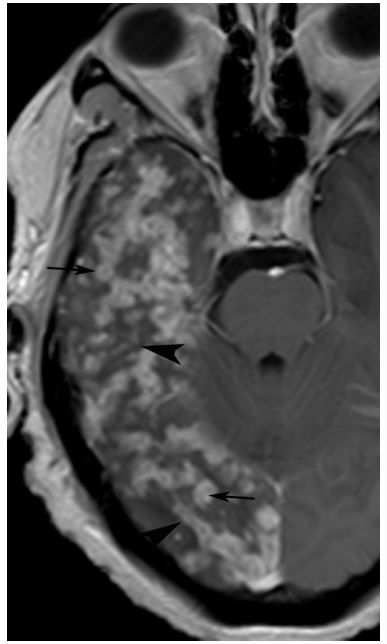


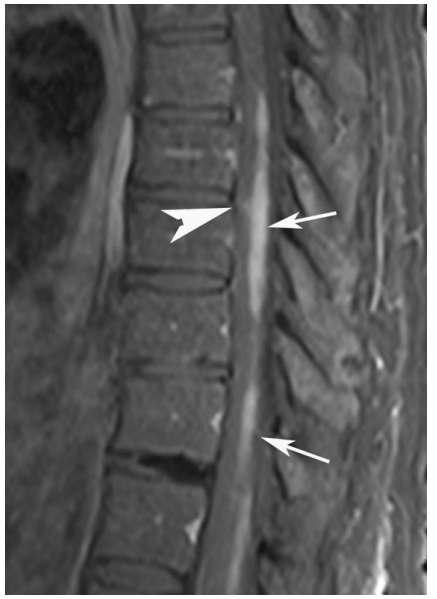
- ~10% prevalence in USA; closer to 50% in Europe and Japan
- Usually is symptomatic
  - Red, painful, blurry vision
- Anterior uveitis (most common)
- Posterior or pan-uveitis (less common)
- Screening: Baseline ophthalmology exam at time of diagnosis
- Eye exam if symptoms develop
- Treatment is always indicated
  - 1st line: Topical steroid drops
  - 2nd line: oral steroids
  - Steroid sparing: MTX, azathioprine, MMF
  - 3rd line: Infliximab

Neurosarcoidosis

- ~5-15% of cases
- Causes ~10% of deaths
- Presenting symptoms varies
  - Headache, facial nerve palsy, seizure (difficult to control)
- Small fiber neuropathy (pain, burning, paresthesia, dysautonomia)
- <u>No screening recommendations</u>

Neurosarcoidosis manifestation[a]	Prevalence
Cranial nerve palsy	31–55%
Chronic aseptic meningitis	16–37%
Spinal cord disease/myelitis	18–23%
Cerebral parenchymal disease	21%
Neuroendocrine (hypothalamo-pituitary) involvement	6–9%
Hydrocephalus	9–10%
Cerebral infarction	6%
Peripheral nervous system	17%





Neurosarcoidosis

- Always requires treatment
  - AMS, visual loss, paralysis, seizure: pulse solumedrol upto 1g/day for 3-5 days followed by taper. Strongly consider adding MTX right away
  - Isolated facial nerve palsy: steroid; rapid 1-2 month taper
  - Small fiber neuropathy: doesn't respond to steroids. Try gabapentin, pregabalin, and duloxetine. Some benefit with anti TNF and IVIG
- Duration of therapy: depending on severity, may be years to life long

Hepatic sarcoidosis

- Most pts are asymptomatic
- Most pts have granuloma on liver biopsy even with normal LFTs
- ~35% have abnormal LFTs
  - Elevation in Alkaline phosphatase very common
  - Abnormal AST/ALT uncommon
- ~6% progress to cirrhosis and 3% develop portal hypertension
- Screening: Check LFTs at time of diagnosis and yearly
- Treatment is generally not indicated
  - Corticosteroids for symptomatic RUQ pain, nausea, weight loss, jaundice
  - Pruritis: ursodeoxycholic acid

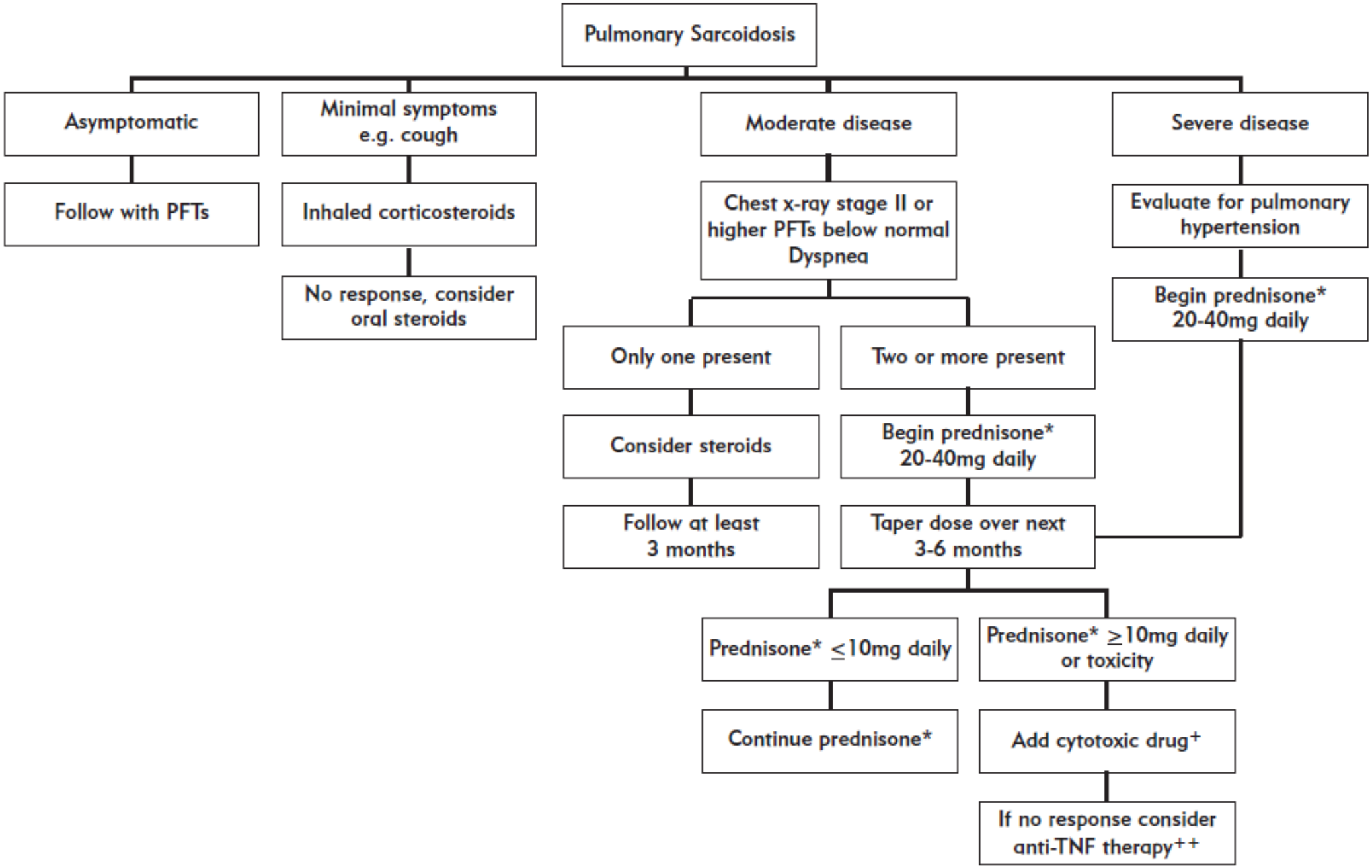
Abnormal Calcium Metabolism

- Mechanism:
  - Overactive macrophages convert 1-OH Vitamin D to 1,25 OH Vitamin D
  - 1,25 OH Vit D promotes hypercalcemia and hypercalciuria
- Common complications:
  - Kidney stones
  - Acute kidney injury or failure
  - Altered mentation, dehydration
- Screening: Serum Ca at time of diagnosis and yearly. Check Vit-D if Ca is high
- Treatment is required if complications or if serum calcium ≥11 mg/dL
  - 1st line: oral steroids (20-30mg/day is usually enough)
  - Steroid sparing: hydroxychloroquine, MTX, azathioprine
  - Non immunomodulatory: ketoconazole

At the first clinic visit

- Thorough history evaluating for exposures/risk factors: inhalational, occupational, medications
- Labs:
  - CBC w/ diff, chem, LFTs, Ca, ACE, IL-2, urine histo, TB quantiferon (skin test less reliable)
  - ANA w/ IFA, ANCA
- Imaging:
  - depends on organ symptoms
- Tests:
  - PFTs (spirometry, lung volume, DLCO) and six minute walk
  - EKG or a holter monitor (if having any palpitations)
- Consults/referrals:
  - Ophthalmology

Questions?


Pulmonary Sarcoidosis
Asymptomatic
Follow with PFTs
Minimal symptoms e.g. cough
Inhaled corticosteroids
No response, consider oral steroids
Moderate disease
Chest x-ray stage II or higher PFTs below normal Dyspnea
Only one present
Consider steroids
Follow at least 3 months
Two or more present
Begin prednisone* 20-40mg daily
Taper dose over next 3-6 months
Prednisone* ≤10mg daily
Continue prednisone*
Prednisone* ≥10mg daily or toxicity
Add cytotoxic drug+
If no response consider anti-TNF therapy++
Severe disease
Evaluate for pulmonary hypertension
Begin prednisone* 20-40mg daily

Agent	Effective dose	Titration	Common side effects	Serious side effects	Monitoring labs	Route
Methotrexate	•10 – 25mg/wk	•Start: 10mg/wk •Increase by 2.5mg/wk	•Alopecia •Dyspepsia •N/V, diarrhea •Transaminitis	•Pneumonitis •Marrow suppression •Hepatitis	•CBC w/ diff, Chem, LFTs monthly until goal dose then q3 months	•Oral •SubQ (abdomen or thigh)
Azathioprine	• ~2mg/Kg/day	• Start 50mg and titrate by 25mg every 2-3 weeks. • Max: 200mg/day	• GI side effects • Lymphopenia	• Pancytopenia	• CBC w/ diff, LFTs monthly during dose escalation, q3 months there after	•Oral
Leflunomide	• 10 – 20mg	• can start at either 10 or 20mg/day	•GI upsets •hepatotoxicity •rash • neuropathy •Headache	• hepatotoxicity	• CBC w/ diff, LFTs monthly x3, then q3 months	•Oral
Hydroxy-chloroquine	•200 – 400mg (no more than 5/mg/kg/day)	•Start 200mg and titrate upto 5mg/kg/day	•Retinopathy	• Retinopathy •Hemolysis	•Eye exam every 6 – 12 months	•Oral
Mycophenolate	• 500 – 1500mg BID	• 500mg BID then increase slowly over several weeks as tolerated	•GI side effects •Leukopenia	• Pancytopenia • Maligancy	• CBC w/ diff, LFTs monthly until goal dose, then q3 months	•Oral
Infliximab	• 5 mg/kg q 4-6 weeks after loading	None	GI side effects Headache Rash Infusion reactions	• Infections • Anaphylaxis • Malignancy	• PPD or quantiferon prior to starting	•Infusion
Adalimumab	• 40 mg q week	None	GI side effects Headache Rash Infusion reactions	• Infections • Anaphylaxis • Malignancy	• PPD or quantiferon prior to starting	•Injection

How do I know if its disease progression or something else?

- Any objective signs of disease progression present?
  - New nodules or GG on CT
  - Reduction in PFTs (10 – 15% drop in FVC or 15 – 20% drop in DLCO)
  - New organ involvement
- Did the patient have hx of abnormal biomarkers?
  - ACE, IL-2, 1, 25 (OH) vit-D, ESR, CRP
- Symptoms
  - Evaluate for comorbid conditions before escalating immunosuppression
    - Asthma, PH (specially if fibrotic sarcoid), CAD, deconditioning

Sarcoidosis Care at OSUMC

Pulmonary:

- Elliot Crouser, MD
- Arindam (AJ) Singha, MD

Cardiology:

- Rami Kahwash, MD

Neurology: Multidisciplinary Neurosarcoidosis Clinic at Martha Morehouse

- Tirisham Gyang, MD

Questions?