



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Granulomatous Lung Disease

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Disclosures

- Nothing to disclose

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- Jefferson Medical College
- Residency at BIDMC
- Pulmonary and Critical Care Medicine Fellowship at the Harvard Combined Program
- Instructor in Medicine at HMS
 - Clinical Focus: interstitial lung disease and intensive care medicine
 - Research Focus: interstitial lung disease

Granulomatous Lung Disease Differential Diagnosis

- Non-Infectious

- Sarcoidosis
- Hypersensitivity pneumonitis
- Chronic beryllium disease
- Hot tub lung
- Vasculitis
- Aspiration pneumonia
- Talc granulomatosis
- Rheumatoid nodule
- Bronchocentric granulomatosis

- Infectious

- Mycobacteria – tuberculosis and nontuberculous mycobacteria
- Endemic fungi – histoplasma, cryptococcus, coccidioides, Blastomyces
- Pneumocystis
- Aspergillus
- Parasites - Dirofilaria

Tuberculous Mycobacterial Disease

- Lungs are the major site of infection
- Pulmonary complications include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis
- Radiographic findings
 - Hilar lymphadenopathy – 65% of cases
 - Pleural effusions – 33% (1/3) of cases
 - Pulmonary infiltrates – 27% of cases

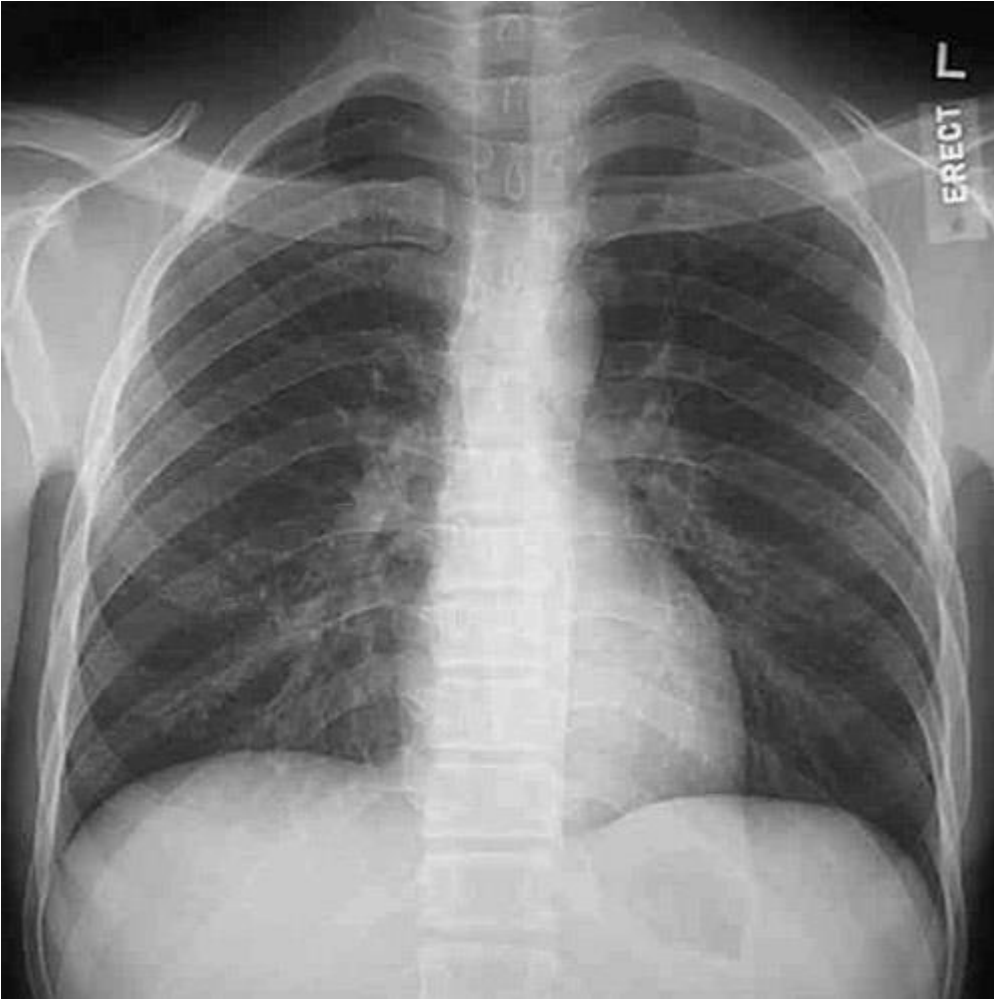
Nontuberculous Mycobacterial Disease

- Pulmonary disease usually caused by *Mycobacterium avium complex (MAC)*, *Mycobacterium abscessus*, and *Mycobacterium kansasii*
 - Geography plays a role in the epidemiology of NTM
- Symptoms vary based on underlying lung disease –cough, fatigue, malaise, weakness, dyspnea, chest pain, and hemoptysis
- Underlying lung disease
 - Smoking and COPD: more common in white, middle-aged or older men
 - Bronchiectasis: older adults (no sex or smoking differences)
- No underlying lung disease
 - Predominantly in non-smoking women over 50

Endemic Fungi

- Often present with mediastinal/hilar lymphadenopathy and pneumonia
- Histoplasma – most common in Midwestern states in the Ohio and Mississippi River Valleys
- Blastomycosis – systemic pyogranulomatous infection, primarily in south-central and upper midwestern United States
- Cryptococcus – worldwide distribution, most common in immune compromised hosts
- Coccidioides – most common in the southwestern United States, especially Arizona and the San Joaquin Valley of California

Endemic Fungi vs Sarcoidosis



<http://ar.utmb.edu/webpath/radiol/pulmrad/pulm021.htm>



<https://radiopaedia.org/articles/thoracic-sarcoidosis-staging>

Hypersensitivity Pneumonitis

- Inflammation in the lungs caused by breathing certain triggers, including chemicals, molds, dust, fungi, and bacteria
- Imaging classically with upper lobe predominant changes including ground glass opacities and centrilobular nodules, more chronic changes including fibrosis and traction bronchiectasis can also be present depending on the duration of disease
- Pathology classically demonstrates loosely formed granulomas that are centered around the airways

Epidemiology

- Prevalence varies by climate, occupational and environmental exposures
- Estimates from available studies: 0.3-0.9 per 100,000 individuals
- Higher incidence in high-risk populations – one study reported that among bird breeders the incidence is 54.6 per 100,000 people
- Insurance claim data show a 1-year prevalence of 1.67-2.71 per 100,000 people in the US
- ILD registry data varies greatly – reported prevalence of ILD cases ranges from 2% to 47%

Methods of Categorization

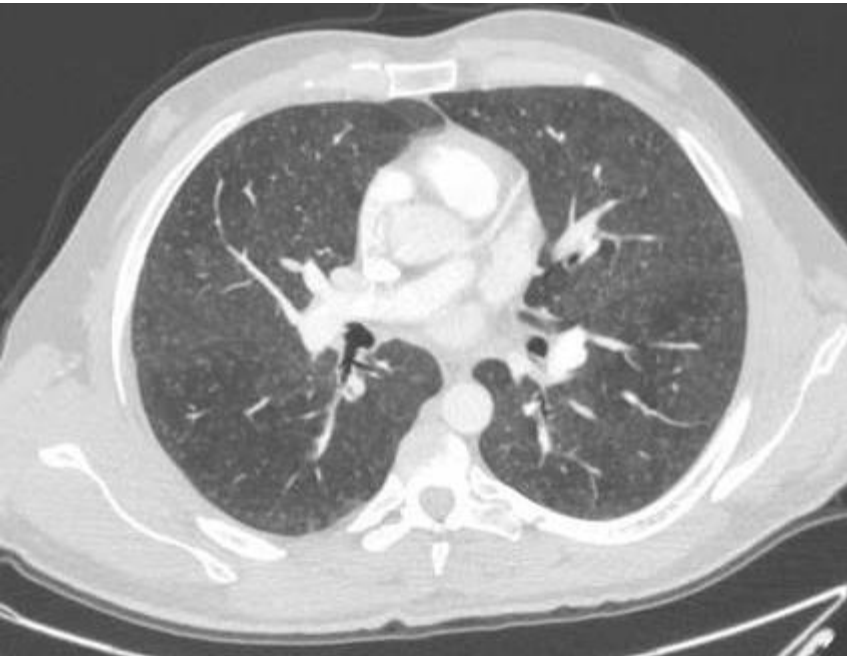
1. Based on the frequency, duration, and intensity of exposure, along with the duration of illness
 - Suggests an evolution of disease
2. Two categories: Nonfibrotic (inflammatory) and Fibrotic (can be mixed inflammatory and fibrotic)
 - Updated in the 2020 ATS/JRS/ALAT guidelines

Classical Classification

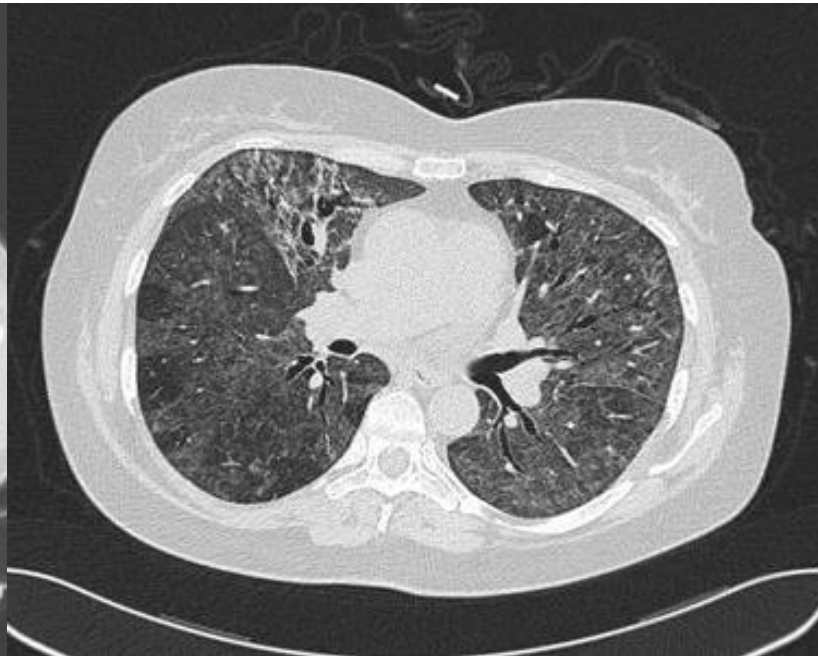
- Acute – often confused with infection, characterized by acute onset (4-6 hours after exposure), improves with removal of exposure
 - Classic board question is “hot tub lung” which occurs due to exposure to nontuberculous mycobacteria
- Subacute – gradual development of symptoms
- Chronic – insidious onset, may lack the history of the acute episodes, imaging characterized by upper lobe predominant ground glass and possible fibrosis (depending on the time course)
 - Classic examples: Bird Fancier’s Disease, Farmer’s Lung

Categories of Hypersensitivity Pneumonitis

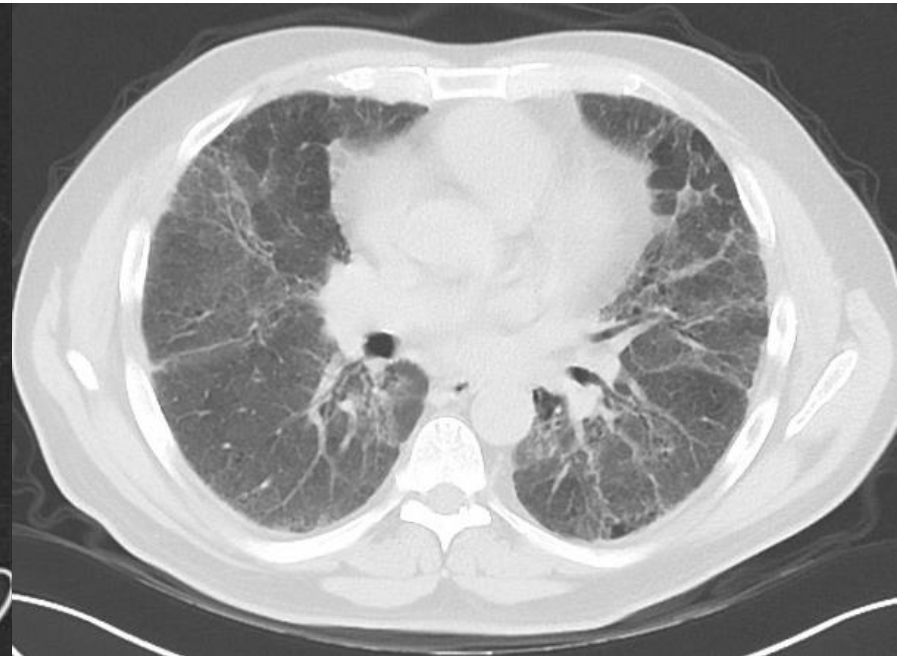
Acute



Subacute



Chronic



Nonfibrotic vs Fibrotic Hypersensitivity Pneumonitis

- Nonfibrotic/Purely Inflammatory: defined by the presence of predominantly inflammatory changes on imaging and/or pathology
 - Patients with this pattern who can avoid ongoing exposure likely have a better prognosis, with either recovery or stability
- Fibrotic: evidence of fibrosis on imaging and/or pathology, can also have an inflammatory component
 - Associated with poor prognosis, especially in the following groups: those with a UIP pattern, persistent exposure or inability to identify the exposure, cigarette smoking, lower baseline vital capacity, lack of BAL lymphocytosis

Evaluation and Diagnosis

- Detailed Exposure History
- Lab Testing: Serologic Assays for specific IgG antibodies – these include precipitin tests, ELISA assays, and automated detection by ImmunoCAP
 - Controversial – sensitivity and specificity vary by the antigen being tested, duration and frequency of exposure, smoking history, and stage of disease
- Bronchoscopy and Biopsy

Detailed Exposure History

- Pets – especially birds, cleaning outdoor bird feeders
- Hobbies – involving feathers, fur, plants, wood or metal workings
- Other feather exposures: comforters, duvets, sleeping bags, jackets
- Water damage to home or place of work
- Hot tub, jacuzzi, sauna, or swimming pool use
- Air conditioning units, humidifiers
- Workplace Exposures (examples) – lab animals, veterinary work, barns/stables, farming, mushroom growing/processing, brewery, winery, metalworking, plastic manufacturing, spray painting, wood working

Treatment

Inflammatory HP:

- Acute HP with mild symptoms – antigen avoidance
- Persistent symptoms – antigen avoidance and corticosteroids
 - Steroid dose is usually prednisone 0.5mg/kg a day x 1 month then a 3 month taper, no change in long term outcomes

Fibrotic HP:

- Chronic HP – antigen avoidance, treatment with corticosteroids or steroid sparing agent (mycophenolate or azathioprine). Progressive fibrosis would qualify for initiation of nintedanib

Salisbury ML, Myers JL, Belloli EA, et al. Am J Respir Crit Care Med. 2017; 196(6):690.

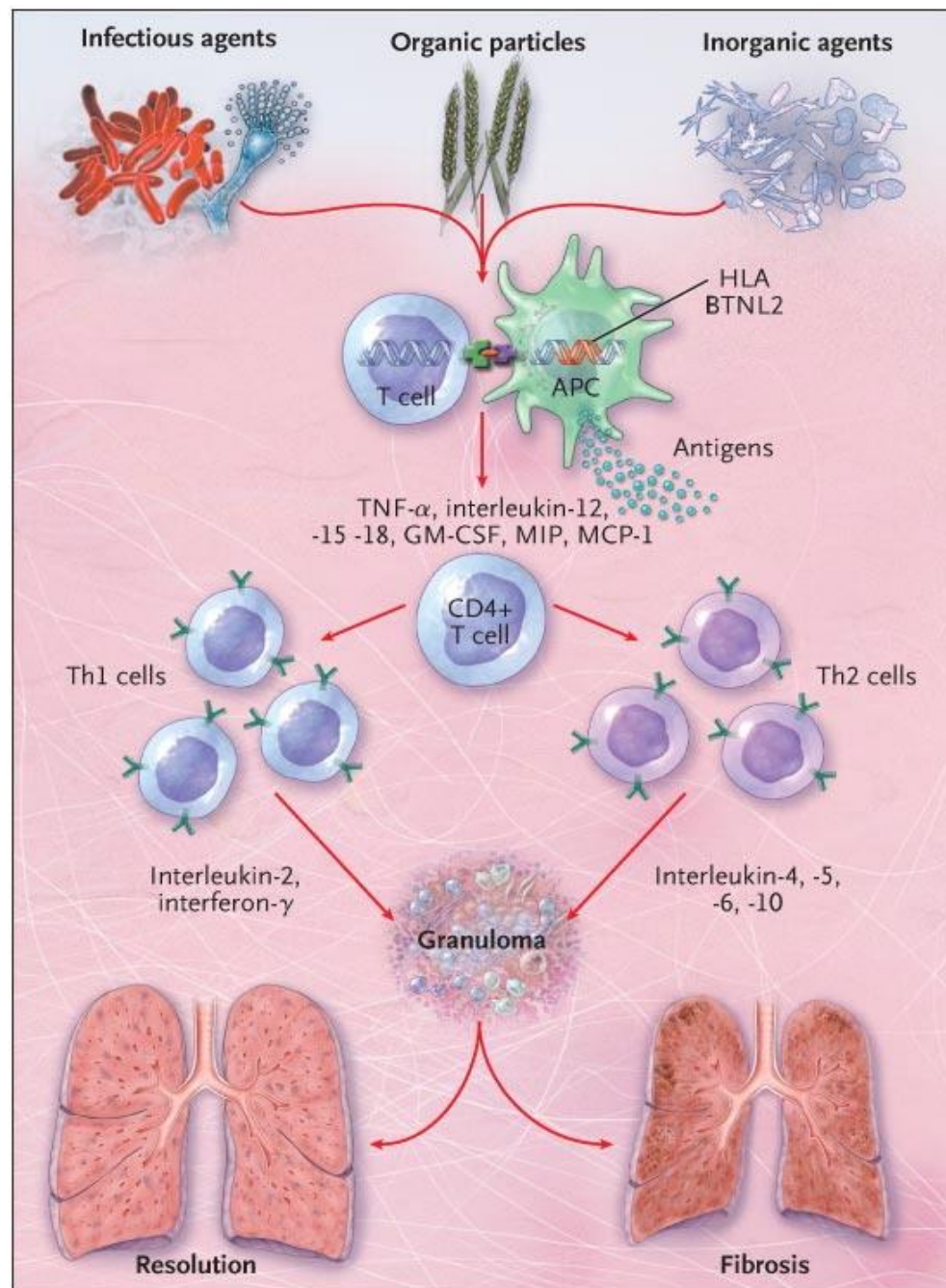
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Flaherty K, Wells A, Cottin V, et al. NEJM. 2019; 381:1718-1727.

Raghu G, Remy-Jardin M, Ryerson C, et al. Am J of Resp Crit Care Med 2020; 202(3):e36.

Sarcoidosis

- Multisystem granulomatous disorder that primarily involves:
 - Lung – 95% of cases
 - Skin – 16% of cases
 - Lymph nodes – 15% of cases
 - Eye – 12% of cases
 - Cardiac – registries note it occurs in about 5% of cases
 - Autopsy studies report a prevalence between 20-60% of cases



Epidemiology

- Prevalence 10 to 20 per 100,000 people
- More common in certain ethnic groups
 - Black Americans ~3-fold greater risk
 - Incidence ratio between 2:1 and 7:1
 - Prevalence ratio between 3:1 and 5:1
- In the US it is more common in women (1.5:1)
- Black Americans – peak prevalence rates 30-39 years of age
- White Americans – flat incidence rates through adulthood

Environmental Risk Factors

- Commonly agreed that there is not one single environmental cause of sarcoidosis
- Fungal Exposure: Higher levels of NAHA (marker of fungal cell biomass) in homes of newly diagnosed sarcoid cases compared to controls
- Mycobacterial antigens – (mKatG) identified more commonly in the serum and tissue of patients with sarcoidosis
- Silicate dust exposure (high levels)

Tercelj M. et al. Environ Health 2011: 10(1): 8.

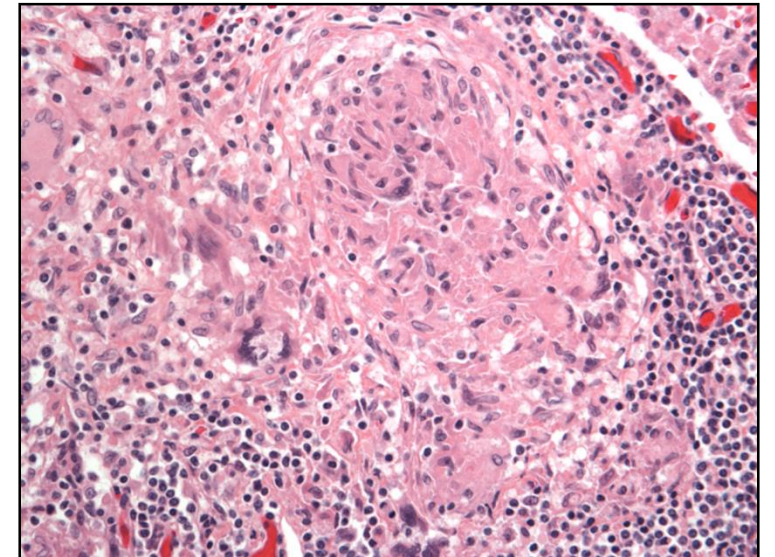
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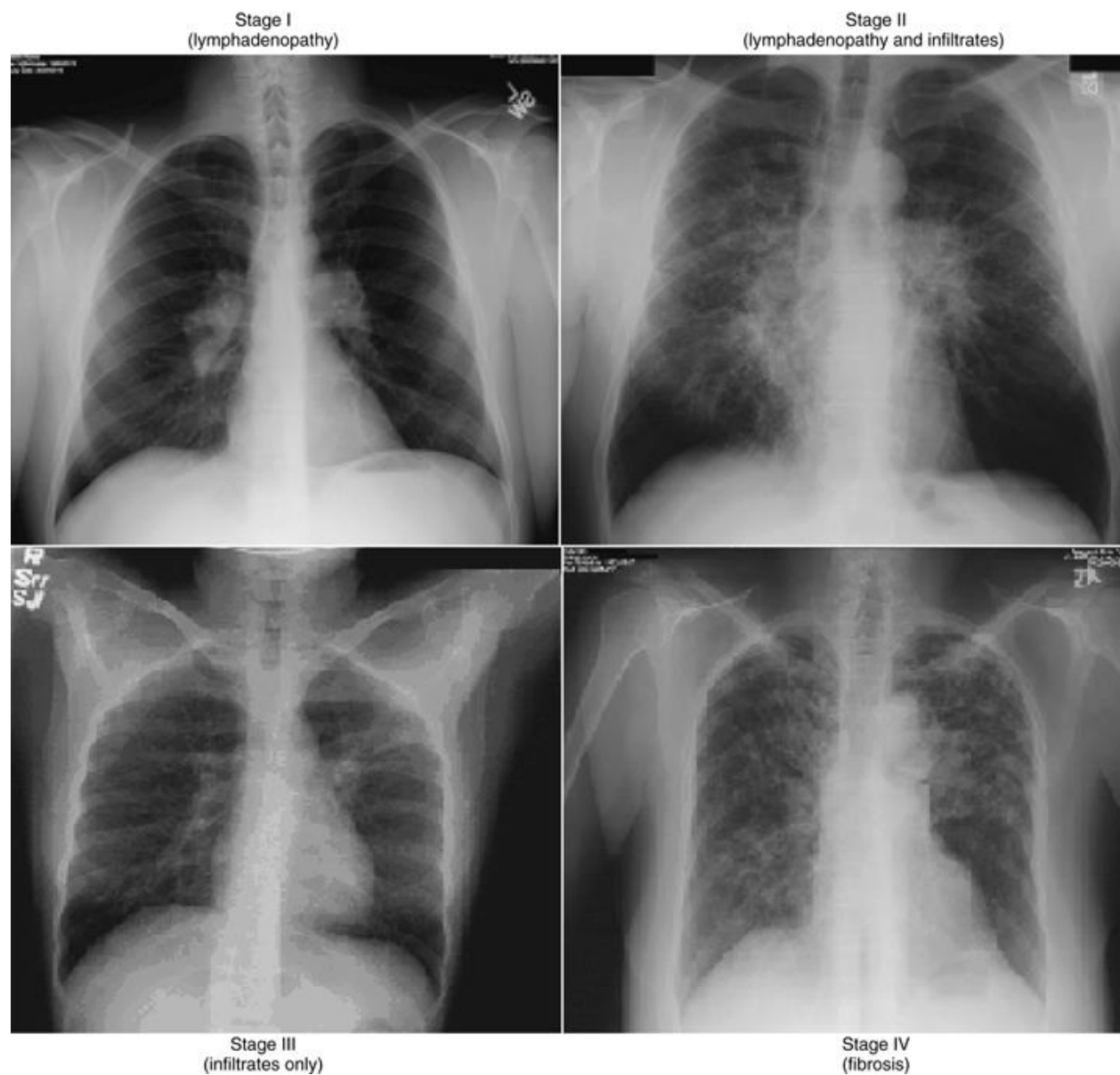
Loupasakis K. et al. J Clin Rheumatol. 2015: 21(1): 19-23.

Diagnosis

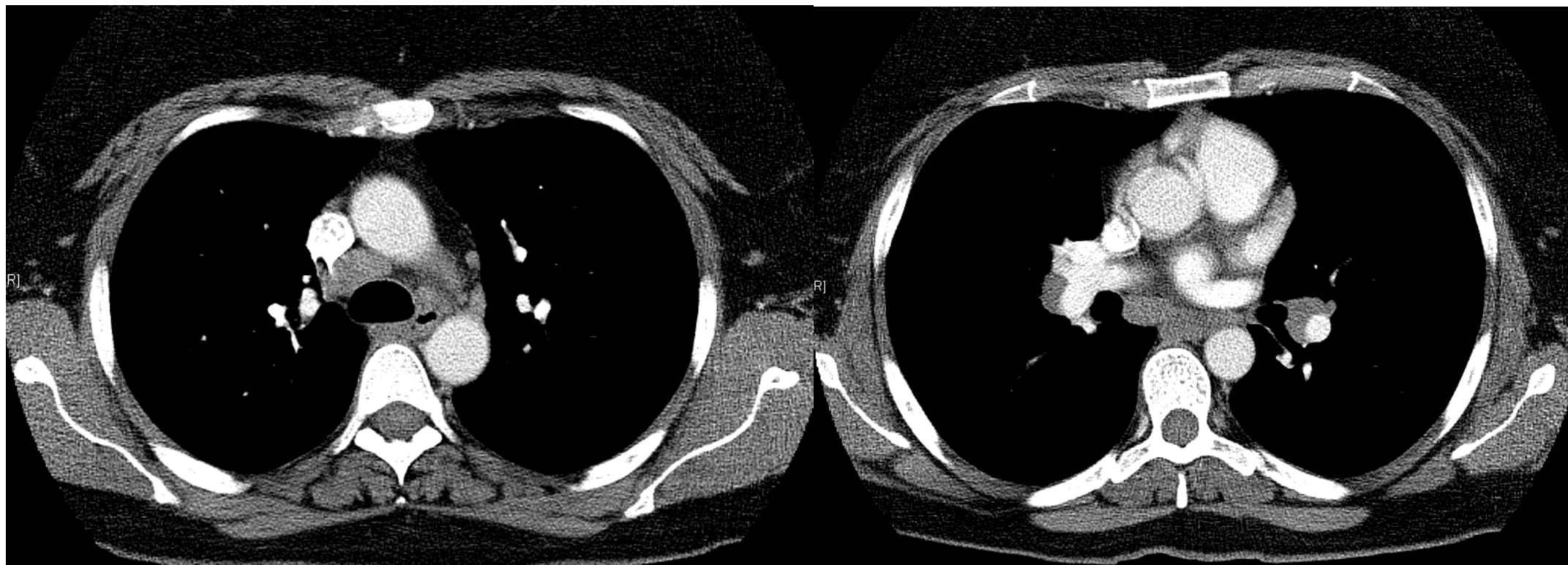
- Compatible clinical and radiological manifestations
- Exclusion of other disease that present similarly
- Histopathologic detection of noncaseating granulomas
- ACE level – should not be used for diagnosis
 - Elevated in ~75% of patients with sarcoidosis
 - Nonspecific
- Transbronchial Lung Biopsy vs. EBUS
 - Diagnostic yield
 - 53% for transbronchial biopsy
 - 80% for EBUS



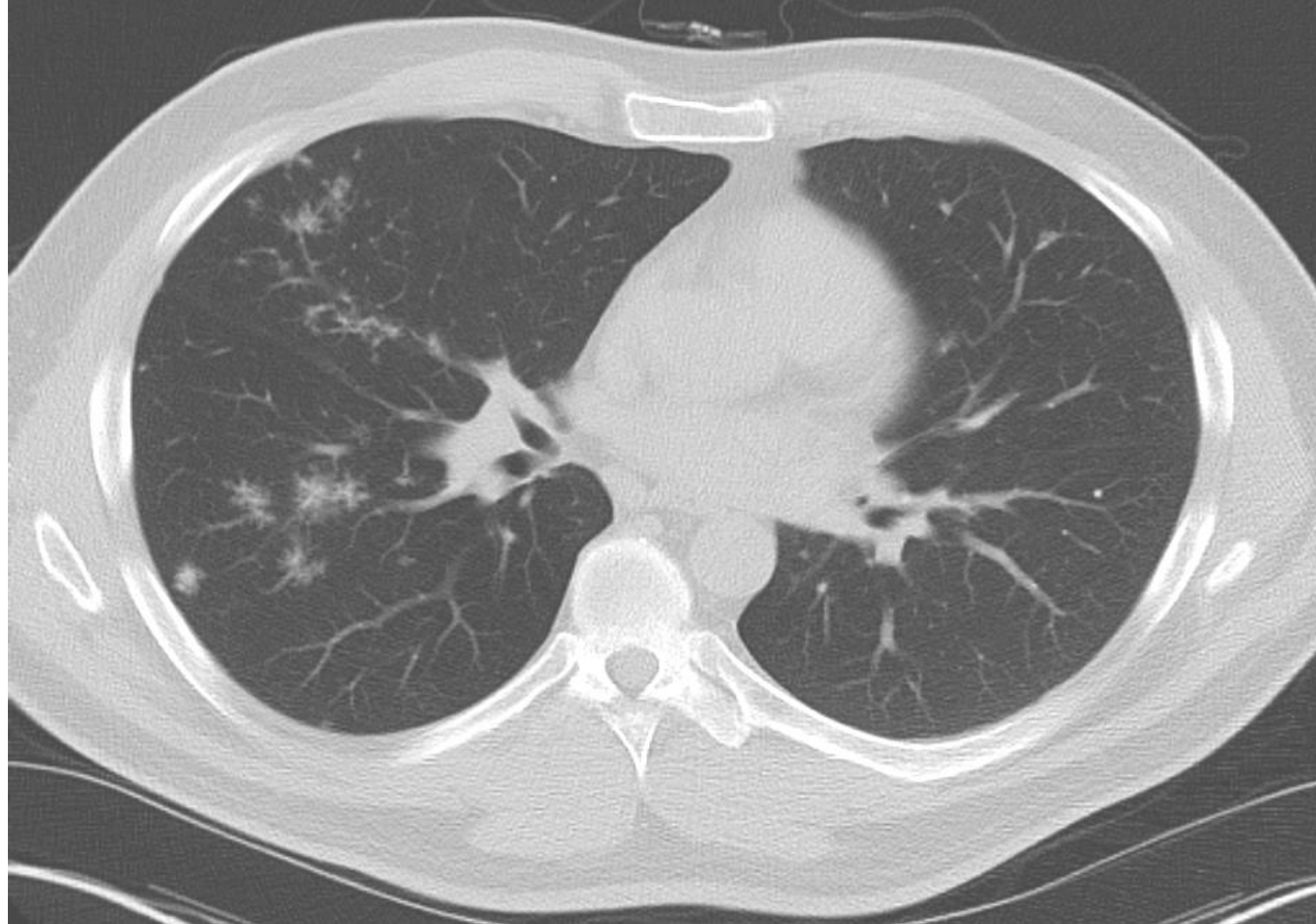
Scadding Stages



Chest CT Characteristics



Chest CT Characteristics



Prognosis

- 452 sarcoid patients from the University of Cincinnati
 - Median age 50 (25-78)
 - Mortality 4% and 9% at 5 and 10 years respectively
- Predictors of Increased Mortality
 - Age
 - Pulmonary Fibrosis
 - Pulmonary Hypertension

Who do we treat?

- Predominantly based on symptoms or evidence of disease progression
 - Limited evidence for disease modifying effect of therapy
 - Declining lung function - no consensus definition

Treatment Options

- Corticosteroids – first line therapy; recommended dose 20-40mg/day
- Steroid refractory, steroid intolerant or unable to taper
 - Methotrexate (15mg/week) with folic acid
 - Azathioprine (2mg/kg daily)
 - Leflunomide (20mg daily)
 - Mycophenolate mofetil
- Refractory Disease
 - Infliximab (3-5mg/kg every 4-6 weeks after loading)
 - Adalimumab (40mg every two weeks)

Clinical Monitoring in Sarcoidosis

- Reasonable Approach Asymptomatic– Every 12-18 months, for at least two years
 - Physical Exam and ROS
 - Labs including calcium, renal and liver function, complete blood count
 - 1,25 dihydroxy vitamin D
 - Pulmonary Function Testing
 - Eye exam
 - EKG
 - ATS suggests that the need for ocular and cardiac examinations be based on symptoms if the baseline exam is normal

Clinical Monitoring in Sarcoidosis

- **Active Disease**
- Every 3-4 Months:
 - Physical Exam and ROS
 - Labs based on disease activity and therapy
- Every 6 Months:
 - Eye exam – if on hydroxychloroquine
- Every 12 Months:
 - Labs including calcium, renal and liver function, complete blood count
 - 1,25 dihydroxy and 25 hydroxy vitamin D
 - Pulmonary Function Testing
 - Eye exam
 - EKG
 - Chest X-ray

Lofgren's Syndrome

- Present in less than 5-10% of patients with sarcoidosis
- Combination of erythema nodosum (EN), hilar lymphadenopathy, migratory polyarthralgias, and fever – more common in women
 - Men often present with bilateral ankle arthritis and *without* erythema nodosum
- The presence of this constellation of symptoms is 95% specific for the diagnosis of sarcoidosis
- Associated with a good prognosis and spontaneous remission

Question 1

- A 24-year-old woman presents for follow up. Six weeks ago, she fell, and a chest x-ray was done for evaluation of pleuritic chest pain. The chest pain has resolved, she denies any shortness of breath, cough, fever/chills, night sweats or weight loss. No joint pain or swelling. Her vital signs and physical exam are within normal limits. Chest x-ray is shown on the next slide.



Question 1

- Which of the following is the most appropriate management?
 - A. Endobronchial ultrasound and biopsy
 - B. High-resolution CT scan of the chest
 - C. Prednisone
 - D. Observation

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Answer

- This patient has stage I sarcoidosis, with no symptoms, so she would not be treated and observation is the most appropriate management

Question 2

- A 22-year-old man presents with acute onset of fever, chills, dyspnea, and nonproductive cough. He is a college student and spends his summers working on a farm, he does not wear a mask. His symptoms worsen during the week to the point that he will miss several days of work, away from work his symptoms improve, then the cycle begins again. On exam his temperature is 100.1, blood pressure is 120/80, heart rate is 98, and respiratory rate is 22. Oxygen saturation is 94% on RA. His lungs have diffuse crackles. Chest x-ray has upper-lobe ground glass opacities.

Question 2

- Which of the following is the most appropriate treatment?
 - A. Counsel the patient not to return to work
 - B. Inhaled glucocorticoids
 - C. Pirfenidone
 - D. Sirolimus

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Answer

- This patient has acute hypersensitivity pneumonitis most likely related to exposures at his new job working on the farm, he currently has mild symptoms, that are improving with antigen avoidance, so he should be counseled not to return to work

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