Sarcoidosis and Hypersensitivity Pneumonitis

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Disclosures

- Nothing to disclose

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

Cormier Y, Lacasse Y. Clin Pulm Med. 1996; 3:72.

Two Proposed Methods of Categorization

1. Based on the frequency, duration, and intensity of exposure, along with the duration of illness
2. Two categories: acute/inflammatory and chronic/fibrotic

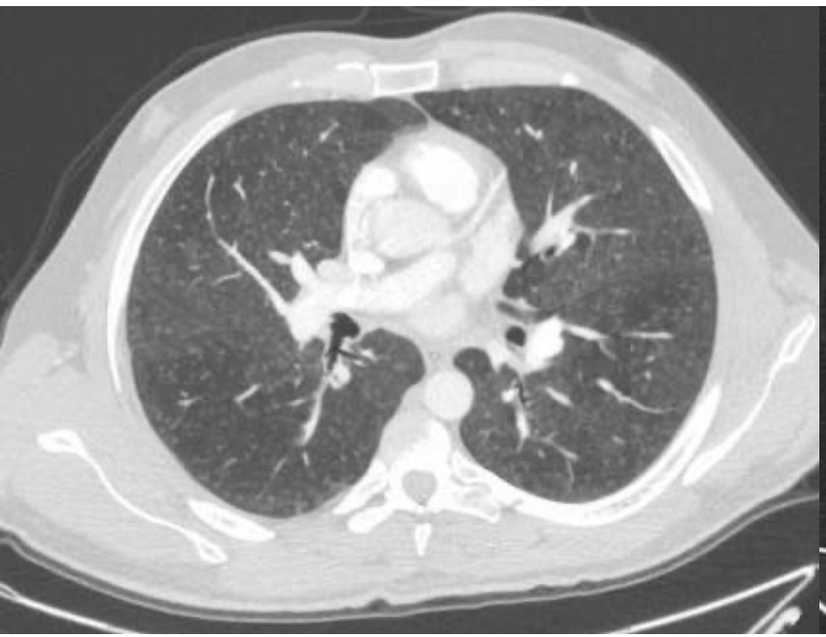
Categories of Hypersensitivity Pneumonitis

- 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

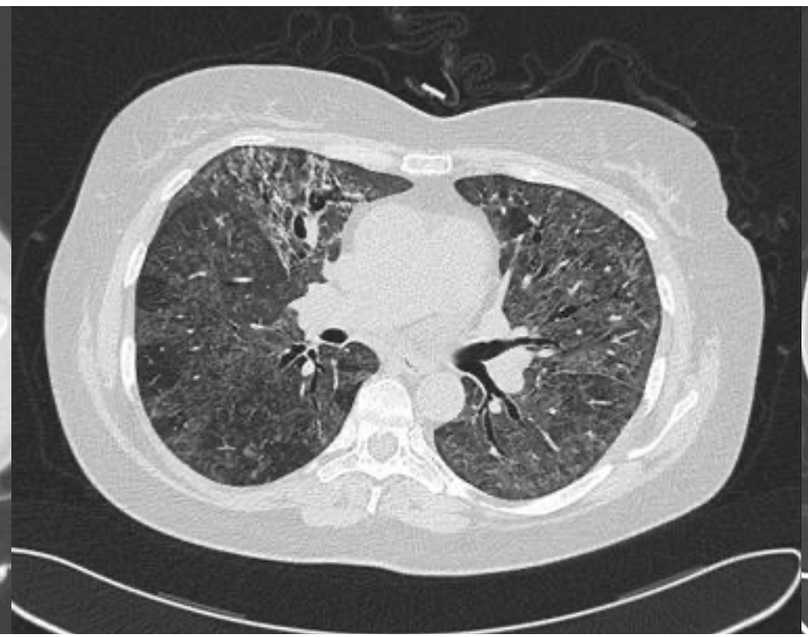
Richerson HB, Bernstein IL, Fink JN, et al. J Allergy Clin Immunol 1989; 84:839.

Categories of Hypersensitivity Pneumonitis

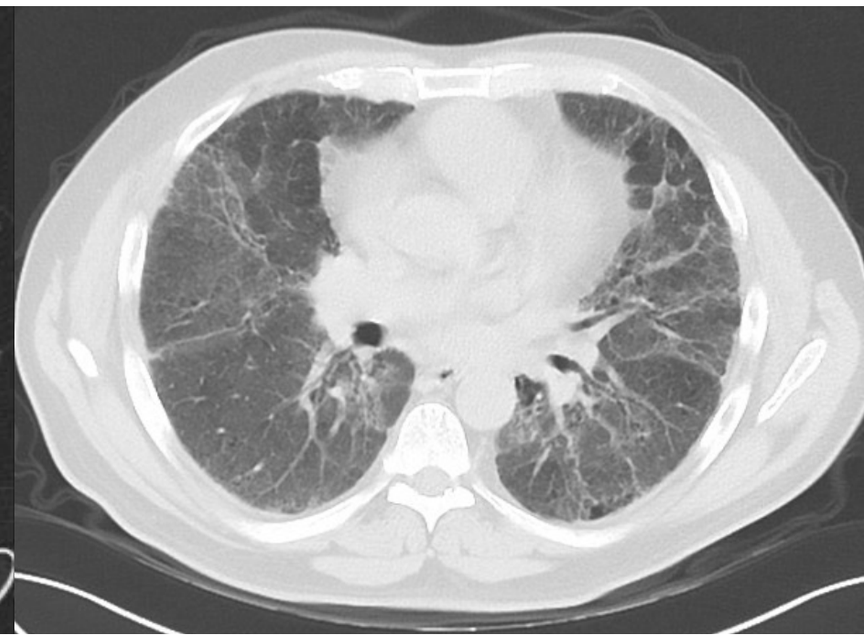
Acute



Subacute



Chronic



Radiopaedia.org

Acute vs Chronic Hypersensitivity Pneumonitis

- Acute/Inflammatory: symptoms for less than six months, reversibility of disease, and predominant imaging finding is ground glass

- Chronic/Fibrotic: symptoms for longer than six months, incomplete reversibility of disease, higher likelihood of progression, and imaging findings include reticular changes, and evidence of fibrosis including traction bronchiectasis and honeycombing

Vasakova M, Morell F, Walsh S, et al. Am J of Resp Crit Care Med 2017; 196(6):680.

Evaluation and Diagnosis

- 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

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
  - *Positive tests are evidence of exposure, not disease as they are often positive in asymptomatic individuals
- Recommended with very low confidence in recent ATS/ALAT/JRS guidelines

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

Bronchoscopy and Biopsy

- Bronchoalveolar lavage (BAL) – marked lymphocytosis, greater than 20% but often over 50%
  - Can be less than 20% in patients with chronic HP
- Transbronchial biopsy – yield is lower in more advanced/fibrotic disease, most studies report a diagnostic yield of 10-40%. Using with BAL increased rate of diagnosis from 27% to 53%
- Cryobiopsy – larger piece of tissue, limited data in HP, but in other diffuse parenchymal lung diseases, diagnostic accuracy is similar to surgical lung biopsy
- Surgical Lung Biopsy – only when a diagnosis cannot be made based on imaging, history, and/or bronchoscopy results

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

Histopathology

- Acute and Subacute / Inflammatory: chronic cellular bronchiolitis with peribronchial lymphocytic inflammation, with small poorly-formed noncaseating granulomas near the respiratory and/or terminal bronchioles, chronic cellular pneumonitis

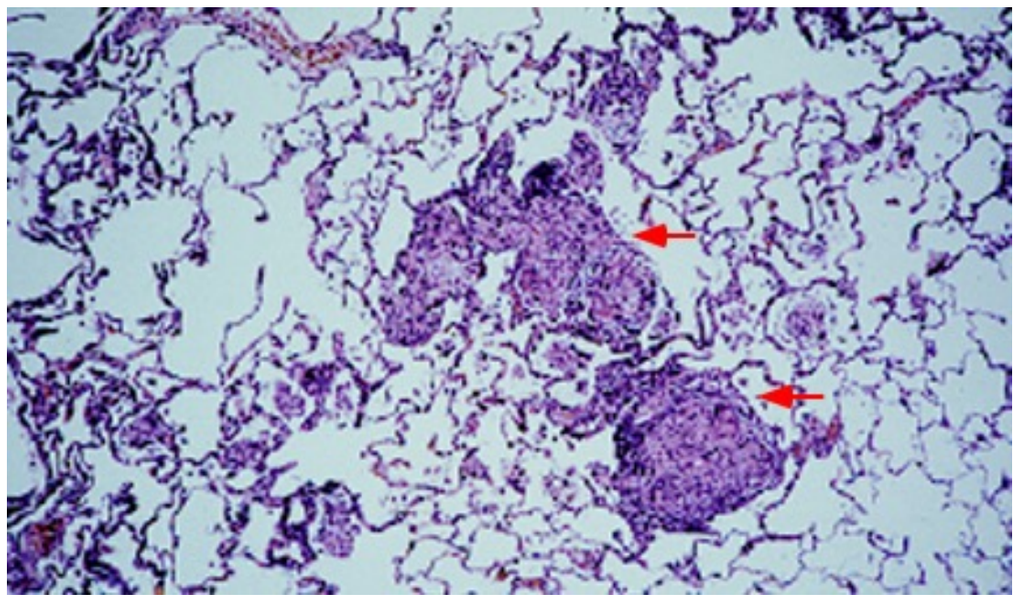
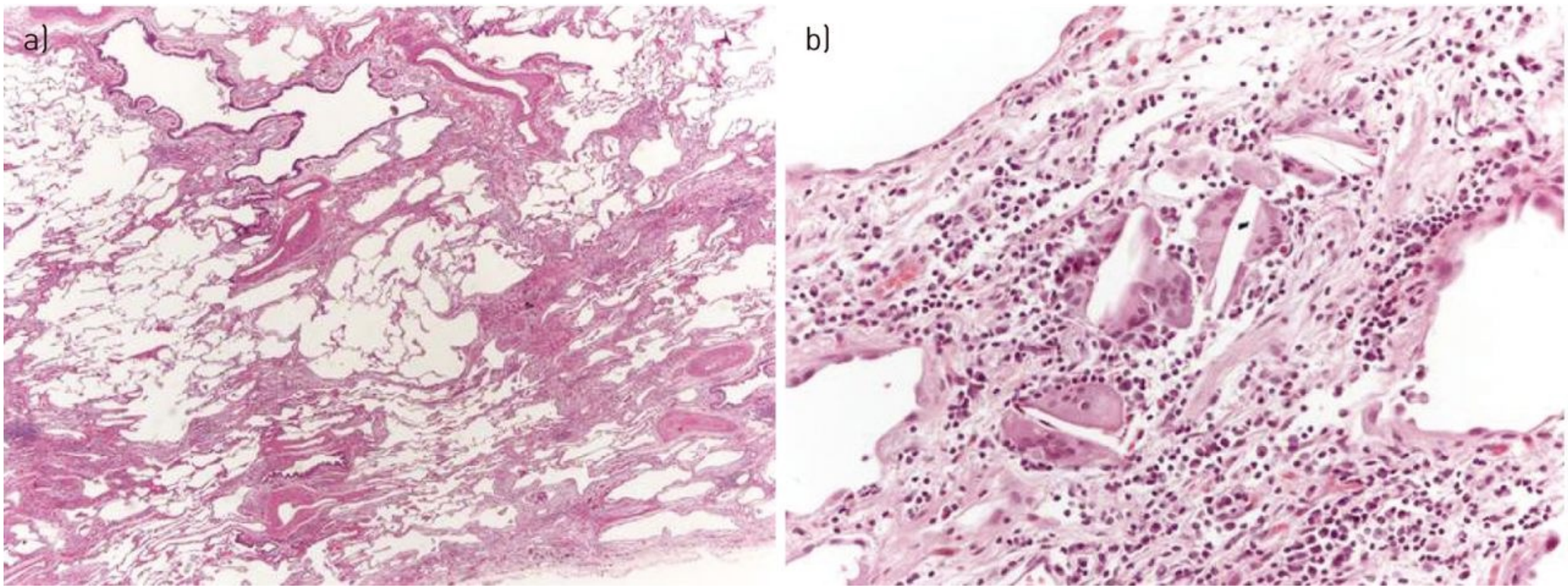


Image from UptoDate, Courtesy of Dr. T. King

Histopathology

- Chronic / Fibrotic: can have features of UIP or fibrotic NSIP and often include poorly or loosely formed granulomas; there can also be areas of organizing pneumonia



Wuyts W, Cavazza A, Rossi G, et al. Eur Resp Rev. 2014; 23: 308-319.

Treatment

Inflammatory HP:

- Acute HP with mild symptoms – antigen avoidance
- Acute/Subacute with 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:

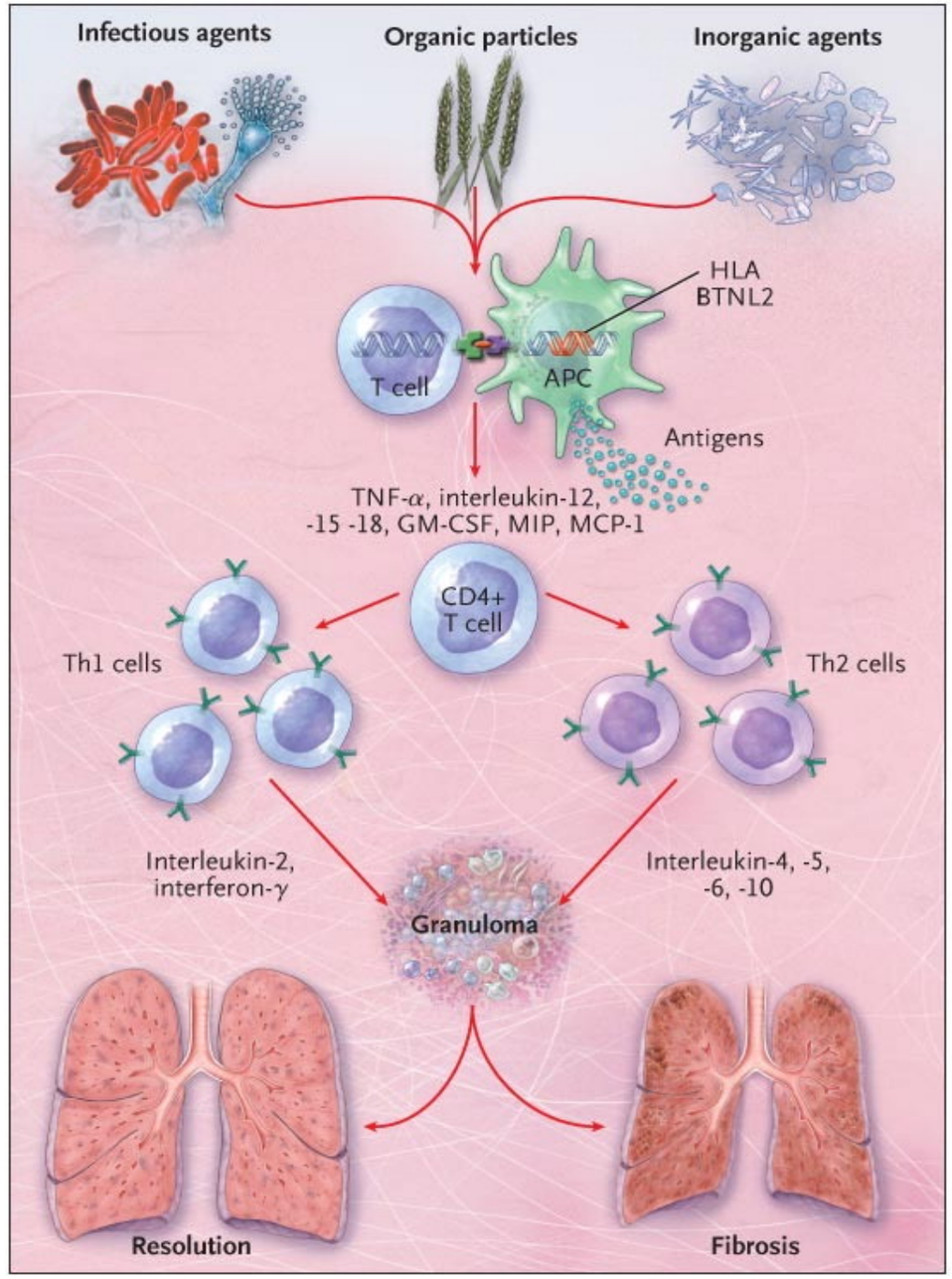
- Chronic HP – antigen avoidance, treatment with corticosteroids or steroid sparing agent (mycophenolate or azathioprine). Progressive fibrosis would qualify for initiation of nintedanib

Salisbury ML, Myers JL, Belloli EA, et al. Am J Respir Crit Care. 2017; 196(6):690.
Morriset J, Johannson KA, Vittinghoff E, et al. Chest. 2017; 151(3):619.
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

Baughman RP et al. Am J Respir Crit Care Med. 2001: 164; 1885-9.
Bernstien M et al. Arch Intern Med. 1999: 44: 721-34.
Tadamura E et al. AJR Am J Roentgenol. 2005: 185(1) 110-5.



Iannuzzi MC et al. N Engl J Med 2007;357:2153-2165.

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

Culver, DA. et al. BMJ. 2019;367:l5553.
Rybicki BA. et al. Am J Epidemiol. 1997: 145(3): 234-41.

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.
Izbicki G et al. Chest. 2007: 131(5); 1414-23.
Drake WP et al. JAMA Dermatol. 2013: 149(9); 1040-9.
Loupasakis K. et al. J Clin Rheumatol. 2015: 21(1): 19-23.

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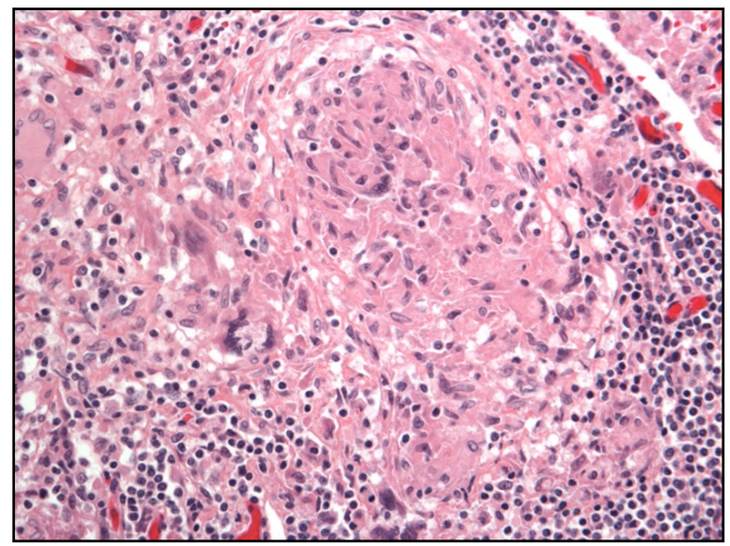
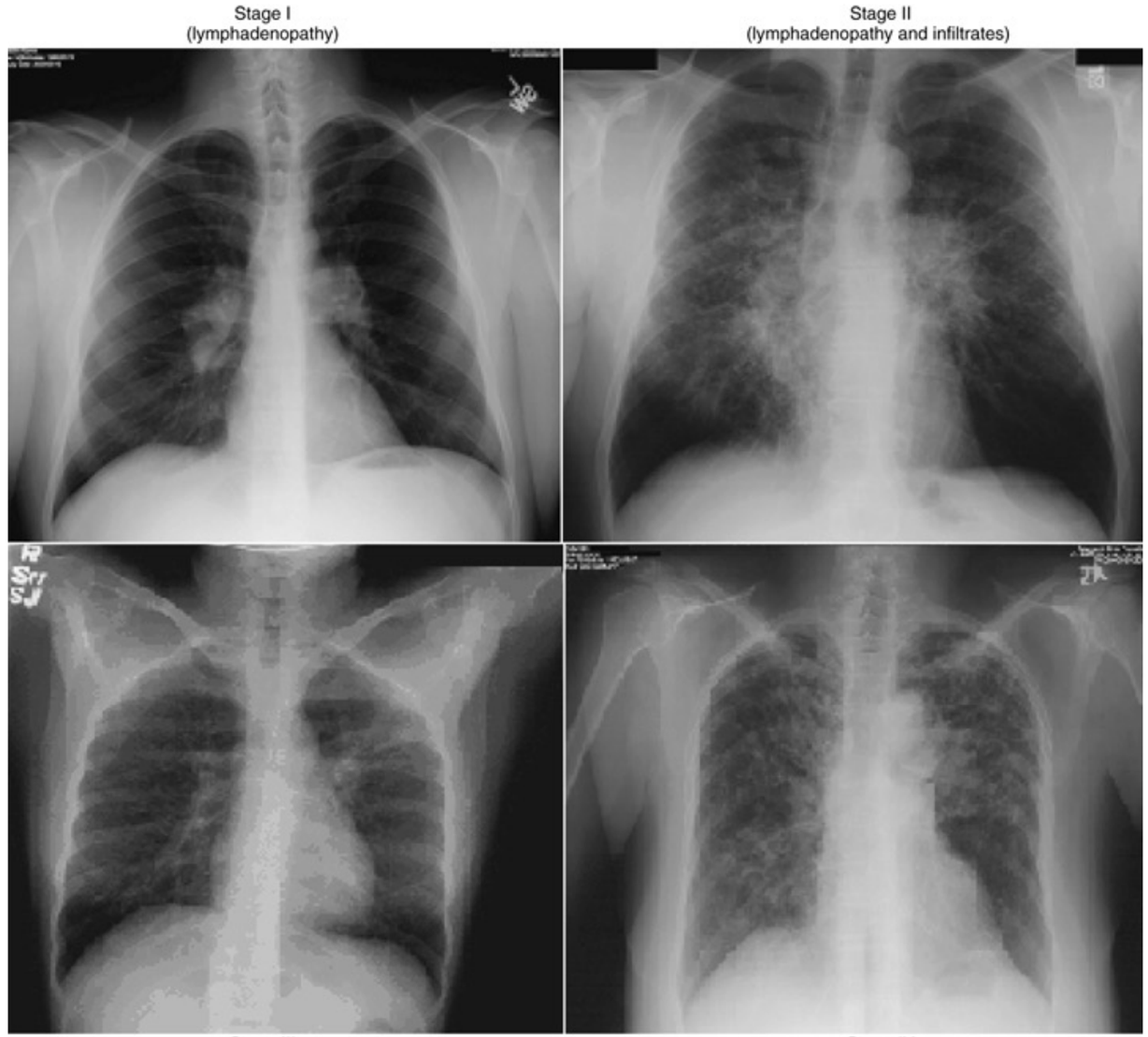
Diagnosis

- 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



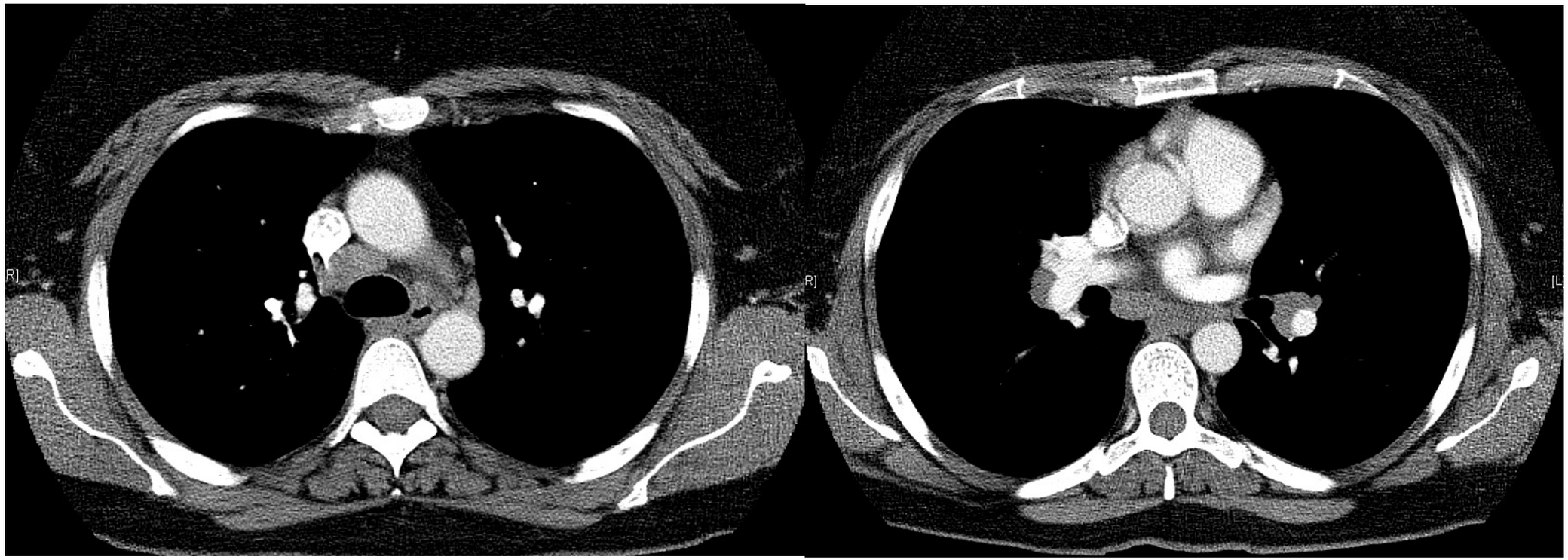
Statement on Sarcoidosis. Am J Respir Crit Care Med. 1999: 160(2); 736-55.

Scadding Stages



http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

Chest CT Characteristics



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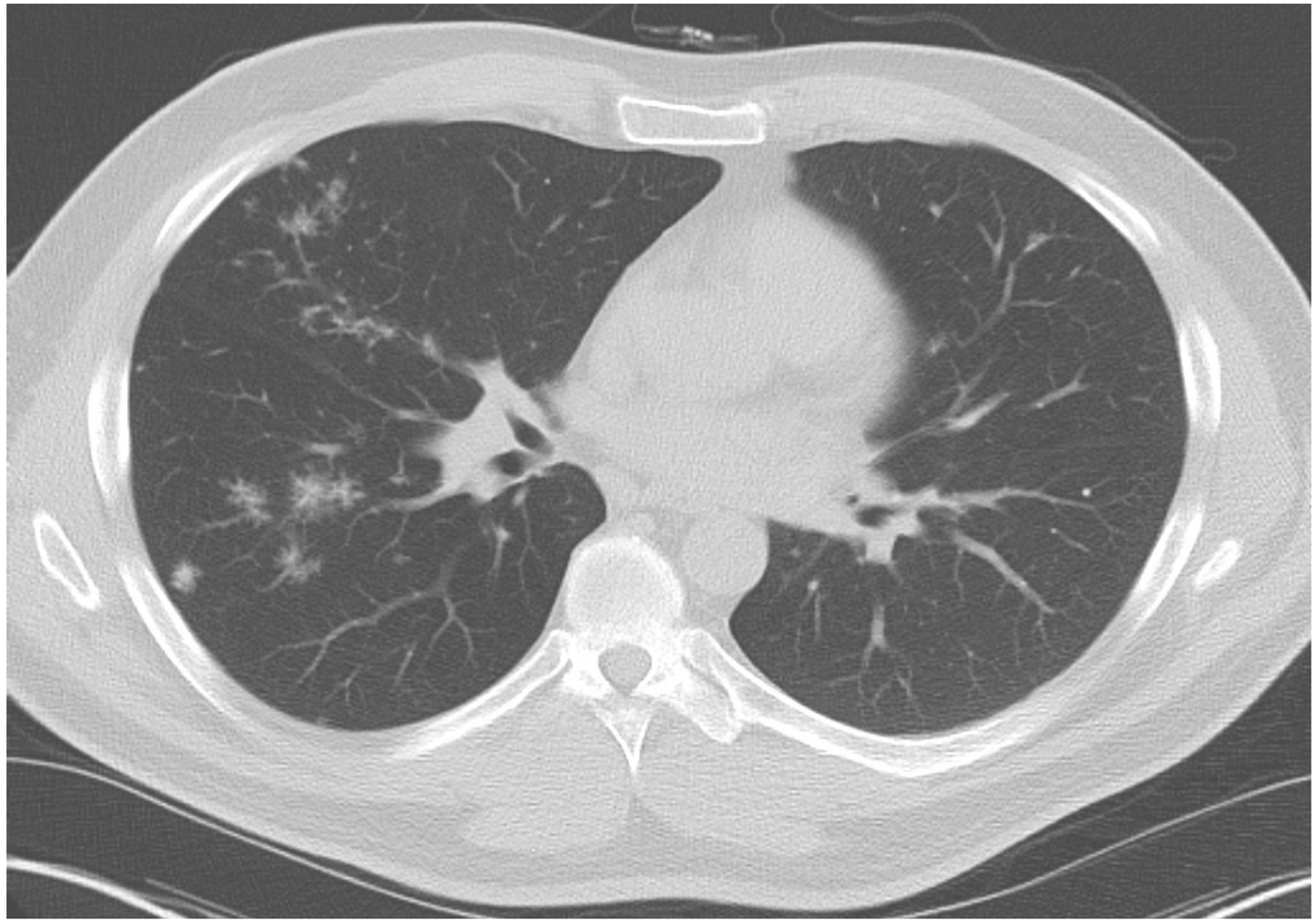


Prognosis

- 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

Kirkil G., et al. Chest 2018 Jan;153(1):105-113.

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

Paramothayan NS. Cochrane Database Syst Rev. 2005: 2: CD002994.
Paramothayan NS. Cochrane Database Syst Rev. 2006: 3: CD03535.

TABLE 1. TREATMENT OF PULMONARY SARCOIDOSIS

- Chest X-ray stage 0/1
  - No symptoms
    - No systemic therapy
      - Level 1A (123)
- Chest X-ray stage 2 to 4
  - Symptomatic
    - Treat with corticosteroids
      - Level 1A (89, 123)
    - Initial dosage of 20–40 mg prednisone or its equivalent
      - Level 1B (89, 124)
    - Treat for 12–24 mo
      - Level 1C (90, 91, 125)
- Steroid-sparing alternatives for chronic pulmonary sarcoidosis
  - Methotrexate
    - Dose of 5–15 mg once a week
      - Level 1A (126–128)
    - Folic acid 1 mg/d may reduce toxicity
      - Level 1B (129)
    - Azathioprine 50–200 mg daily
      - Level 1B (130, 131)
    - Leflunomide 10–20 mg daily
      - Level 1B (132)
    - Mycophenolate
      - Level 1C (101, 133, 134)
- Treatment of refractory sarcoidosis
  - Infliximab intravenously 3–5 mg/kg initially, 2 wk later, then once a month
    - Level 1A (18, 98)

Level A: At least one double-blind, placebo-controlled trial with positive results with one or more case series supporting the results. Level B: Majority of case series showing positive results. Level C: Case series with mixed reports of effectiveness, or only a small number of cases reported. 1A = strong recommendation; 1B = strong recommendation; 1C = strong recommendation; 2A = weak recommendation; 2B = weak recommendation; 2C = weak recommendation. Scoring level of evidence as proposed by Guyatt and coworkers (94).

Baughman RP et al, Am J Respir Crit Care Med. 2011: 183(5): 573-81.

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

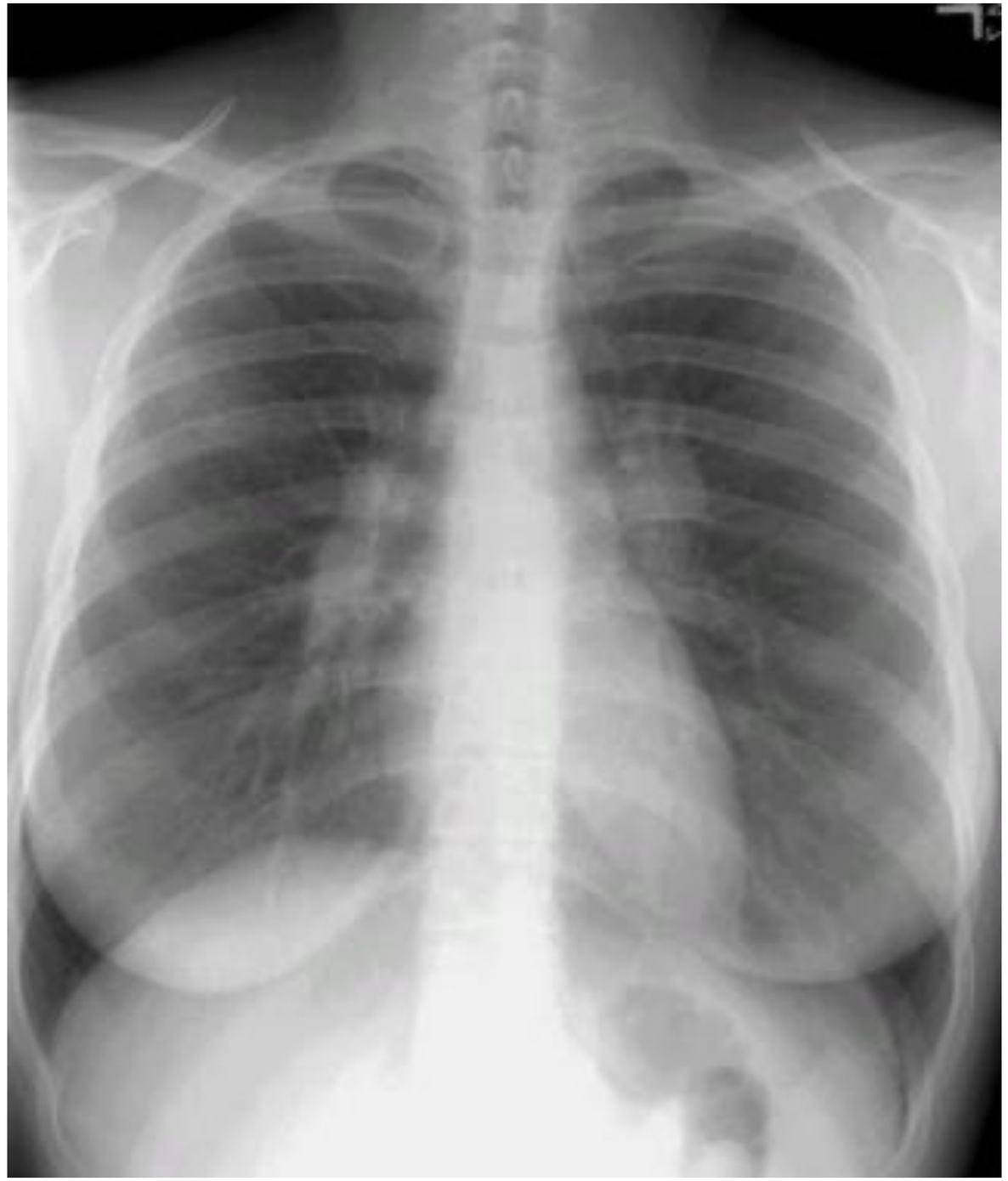
Lofgren's Syndrome

- 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

Grunewald J, Eklund A. Am J Respir Crit Care Med. 2007;175(1):40.

Question 1

- A 24-year-old woman presents for follow up. Six weeks ago, she fell and had a chest x-ray done in the ER 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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Question 2

- A 22-year-old man presents with fever, chills, dyspnea, and nonproductive cough. He is a college student and spends his summers working on a farm. His symptoms worsen during the week to the point that he will miss a few days of work. When he is away from work his symptoms improve, the cycle begins again when he returns to work. 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 crackles throughout. 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. Mycophenolate
C. Nintedanib
D. Prednisone

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Questions?