# Pulmonary Fibrosis and Sarcoidosis

Hiren J Mehta MD
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of Florida

# Disclosures

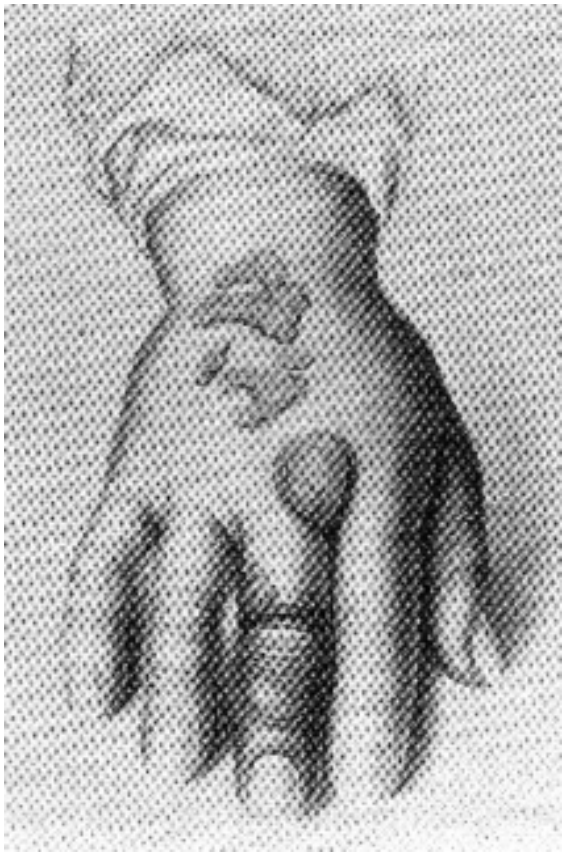
- None pertaining to the talk

# Objectives

- Review the current classification of the most common causes of interstitial lung disease
- Outline the clinical evaluation of interstitial lung disease
- Provide an update on the assessment and treatment of sarcoidosis
- Review the mortality and morbidity of sarcoidosis by stage and the impact of associated airflow obstruction and extra-pulmonary manifestations on mortality

# First Description

*Jonathan Hutchinson*
*1828-1913*



"…I prefer to recognize it, by the name of one of its subjects, as Mortimer's Malady."

Willams, *Sarcoidosis* 1985

# History

| | | | |
|---|---|---|---|
| | Hutchinson | Mortimer's Malady | (face and skin lesions) |
| 1889 | Besnier | Violaceous skin of face | (lupus pernio) |
| 1899 | Boeck | Non-caseating granulomas | (adenopathy, skin nodules) |
| 1914 | Schaumann | Systemic Disorder | |
| 1940's-50's | Lofgren | Spontaneously Resolving Syndrome | |
| 1950's | Kveim-Siltzbach | | |
| 1970's | Lung Immunology – Bronchoalveolar Lavage | | |

# ATS/ERS/WASOG Statement on Sarcoidosis

"…a multisystem disorder of unknown cause(s)… frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscle, bones, and other organs may also be involved."

*AJRCCM* 1999;160:736

# Epidemiology

# ACCESS

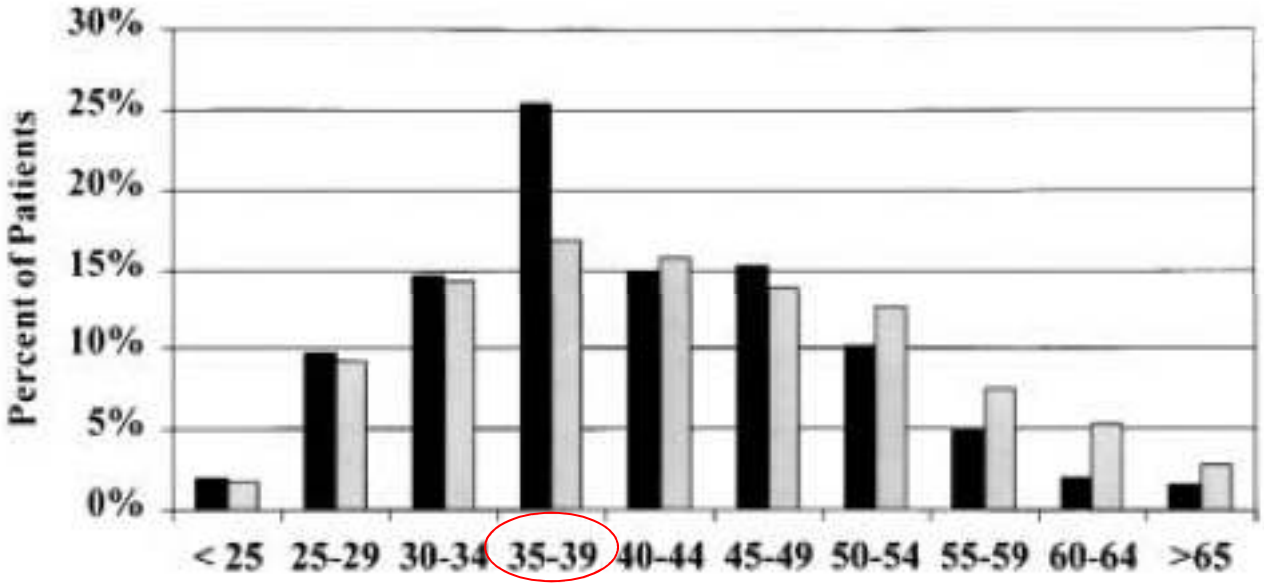



TABLE 2. DISTRIBUTION OF CASES BY SEX AND ETHNIC ORIGIN

| | White | Black | Other | Percent |
|---|---|---|---|---|
| Female | 223 | 234 | 11 | 63.6 |
| Male | 170 | 91 | 7 | 36.4 |
| Percent | 53.4 | 44.2 | 2.4 | |

Baughman et al. *AJRCCM* 2001

**Table 1 Variations in Sarcoidosis Incidence, Presentation, and Genetic Associations across Ethnic Groups**

| Ethnic Group | Incidence per 100,000 | Peak Decade of Incidence | Percent Increased Risk in Females | Typical Clinical Presentation and Course | Recent Reported Genetic Associations |
|---|---|---|---|---|---|
| European Americans | 3–10 | 4th–5th | 10–20 | Stage I, acute course | *BTNL2*,[10] *HLA-DRB1*[4] |
| African Americans | 35–80 | 3rd–4th | 30 | Stage I–II, extrathoracic involvement | *HLA-DRB1*,[4] *HLA-DQB1*,[7] IGKV[11] |
| Northern Europeans | 15–20 | 3rd | 30 | Stage I, acute course | *HSP70-hom*,[12] *BTNL2*,[8] *NRAMP1*,[13] *TAP2*[14] |
| Southern Europeans | 1–5 | 4th–5th | 33 | Löfgren's syndrome | *NOD2*,[15] *CR1*[16] |
| Japanese | 1–2 | 3rd | 10–20 | Ocular involvement, responsive to therapy | *IL-18*,[17] *IFNA17*,[18] *VEGF*,[19] *CCR2*[9] |

- More common: Scandinavian, Irish, German, and West Indian
- Rare: Japanese, Spanish, Portuguese
- African American have 2.4% lifetime risk vs 0.85% for White Americans
- Adjusted incidence in the US 10 to 35 cases per 100,000

Rybicki et al. *Semin Respir Crit Care Med* 2007

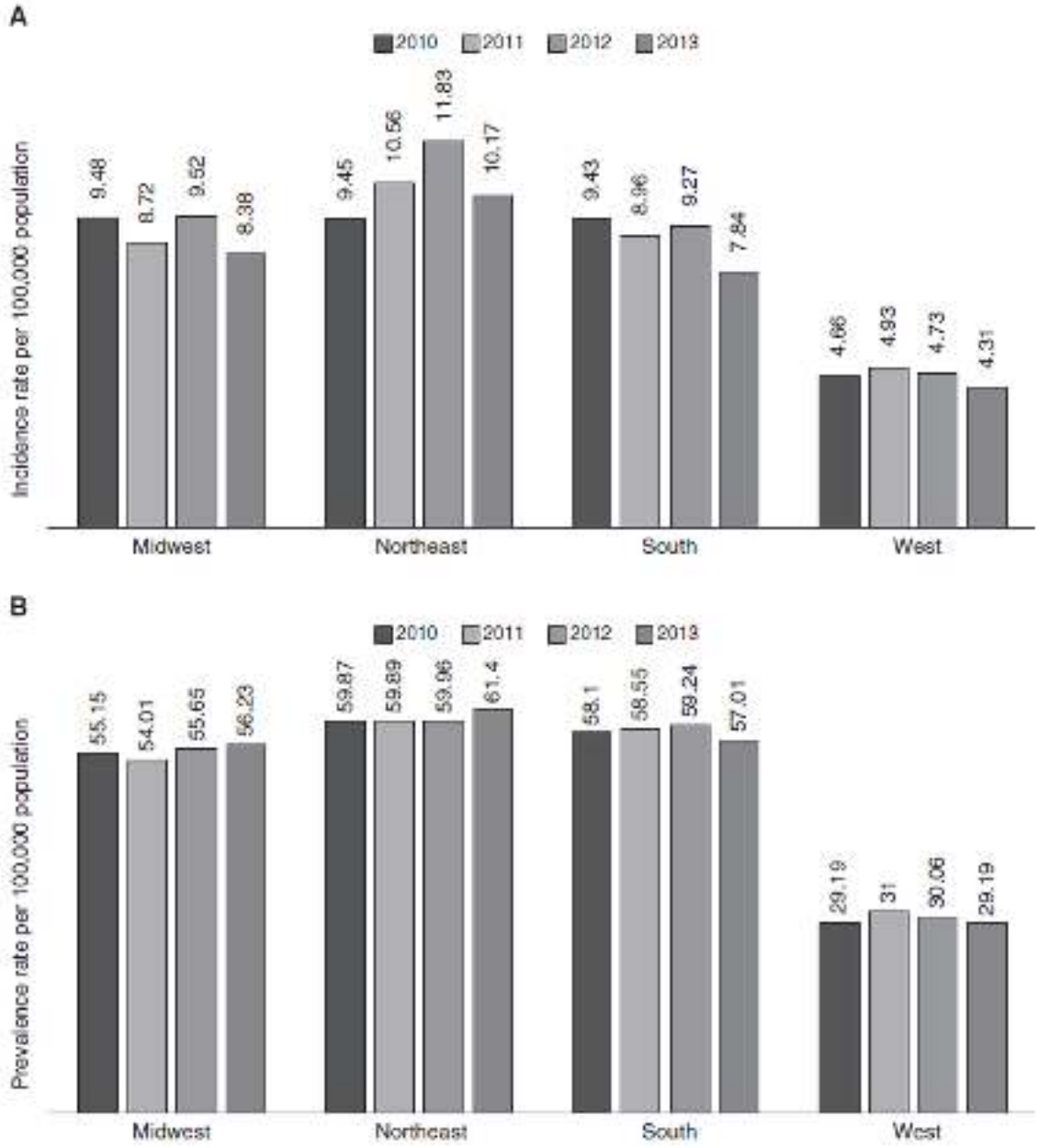



**Figure 4.** The (A) incidence and (B) prevalence of sarcoidosis per insured U.S. residence in 2012 versus geographic area. Patients for whom the region was not specified are not shown. Patients must have been 18 years of age or older and engaged in the affiliated health plan, seen at least twice, been appropriately diagnosed, and been correctly coded. Rates were determined on the basis of all eligible patients in the Optum database.

# Sarcoidosis in Women

- Prevalence in women: 100/100,000
- Incidence increases with age

**Table 1.** Prevalent sarcoidosis (before 1989) in women according to demographic and geographic characteristics at baseline, Nurses' Health Study II

| | Total | n cases | Prevalence * | Age-adjusted OR | | Mutually adjusted OR | |
|---|---|---|---|---|---|---|---|
| | | | | OR | CI | OR | CI |
| Race | | | | | | | |
| White | 111,230 | 102 | 92 | 1 | - | 1 | - |
| Black | 2,308 | 12 | 519 | **5.24** | **2.87-9.55** | 5.34 | 2.92-9.77 |
| Other | 2,892 | 2 | 69 | - | - | - | - |
| Ethnicity | | | | | | | |
| Non-Hispanic | 114,270 | 116 | 102 | - | - | - | - |
| Hispanic | 2,160 | 0 | - | - | - | - | - |
| US geographic region† | | | | | | | |
| West | 17,126 | 13 | 75 | 1 | - | 1 | - |
| Midwest | 38,478 | 30 | 78 | 1.16 | 0.60-2.22 | 1.18 | 0.61-2.31 |
| South | 20,404 | 19 | 93 | 1.38 | 0.68-2.81 | 1.32 | 0.64-2.73 |
| Northeast | 40,225 | 54 | 134 | **1.90** | **1.04-3.48** | **1.92** | **1.02-3.59** |

* Cases per 100,000. OR – Odds Ratio; CI – Confidence Interval. Results in bold are statistically significant. †At baseline, NHSII participants resided in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas).

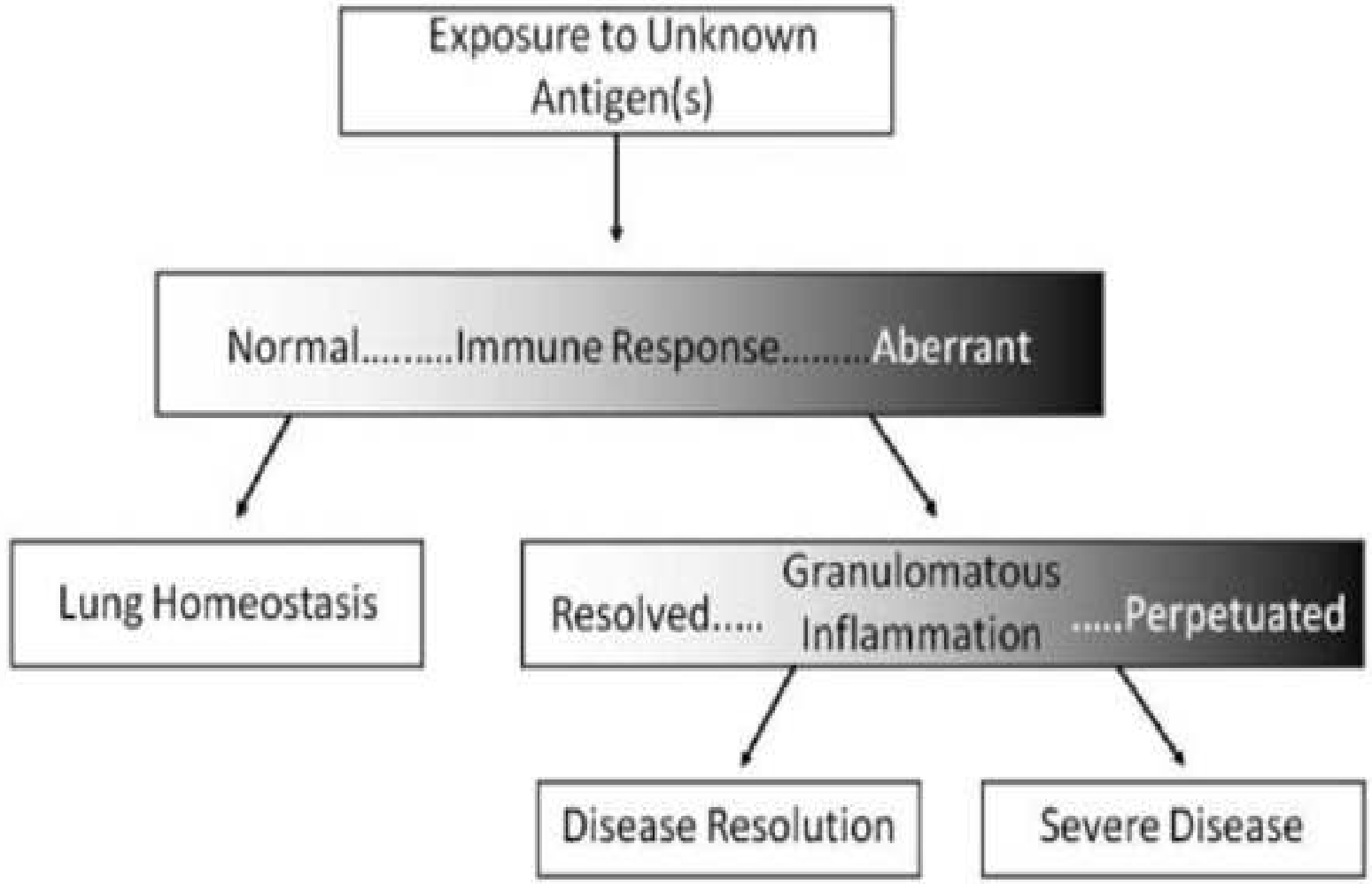
Dumas et al. *AnnalsATS* 2015

# Black Women's Health Study

- Black women experience the highest incidence of sarcoidosis in the US
- Lifetime risk of 2.7% vs 1% for White women
- Average annual incidence of 71/100,000 and prevalence of 2%

Cozier et al. *CHEST* 2011

# Etiology




**Genetic variants may influence progression from each stage to next**

Courtesy of Lisa Maier

# Etiology

- T- helper 1 cell biased disorder
- Genetically predisposed
- Exposed to yet unknown environmental trigger(s) acting as antigens

# Microorganisms

- Virus and bacteria
  - Microorganisms have not been identified by histologic staining or culture
  - Molecular techniques have been more successful

**Table 1**
**Evidence for etiologic agents in sarcoidosis pathogenesis**

| Etiology | Evidence |
|---|---|
| Mycobacteria | M, I, E[18–22,27,29,30] |
| Propionibacteria | M, I[13–15,24–26] |
| Fungal antigens | M[66] |
| Autoantigens | M, I[45,46] |

*Abbreviations:* E, epidemiologic; I, immunologic; M, molecular.

Celada et al. *Clin Chest Med* 2015

# Occupational and Environmental Factors

- Occupation
  - Healthcare workers
  - Teachers
  - Firefighters
  - Navy recruits
  - Agriculture workers
  - World Trade Center disaster responders
- Environment exposures
  - Mold
  - Birds
  - Pesticides
  - Heavy metals

Newman et al. *NEJM* 1997
Prezant et al. *CHEST* 1999
Gorham et al. *Mil Med* 2000
Barnard et al. *J Occup Environ Med* 2005
Crowley et al. *Am J Ind Med* 2011
Jordan et al *J Occup Environ Med* 2011

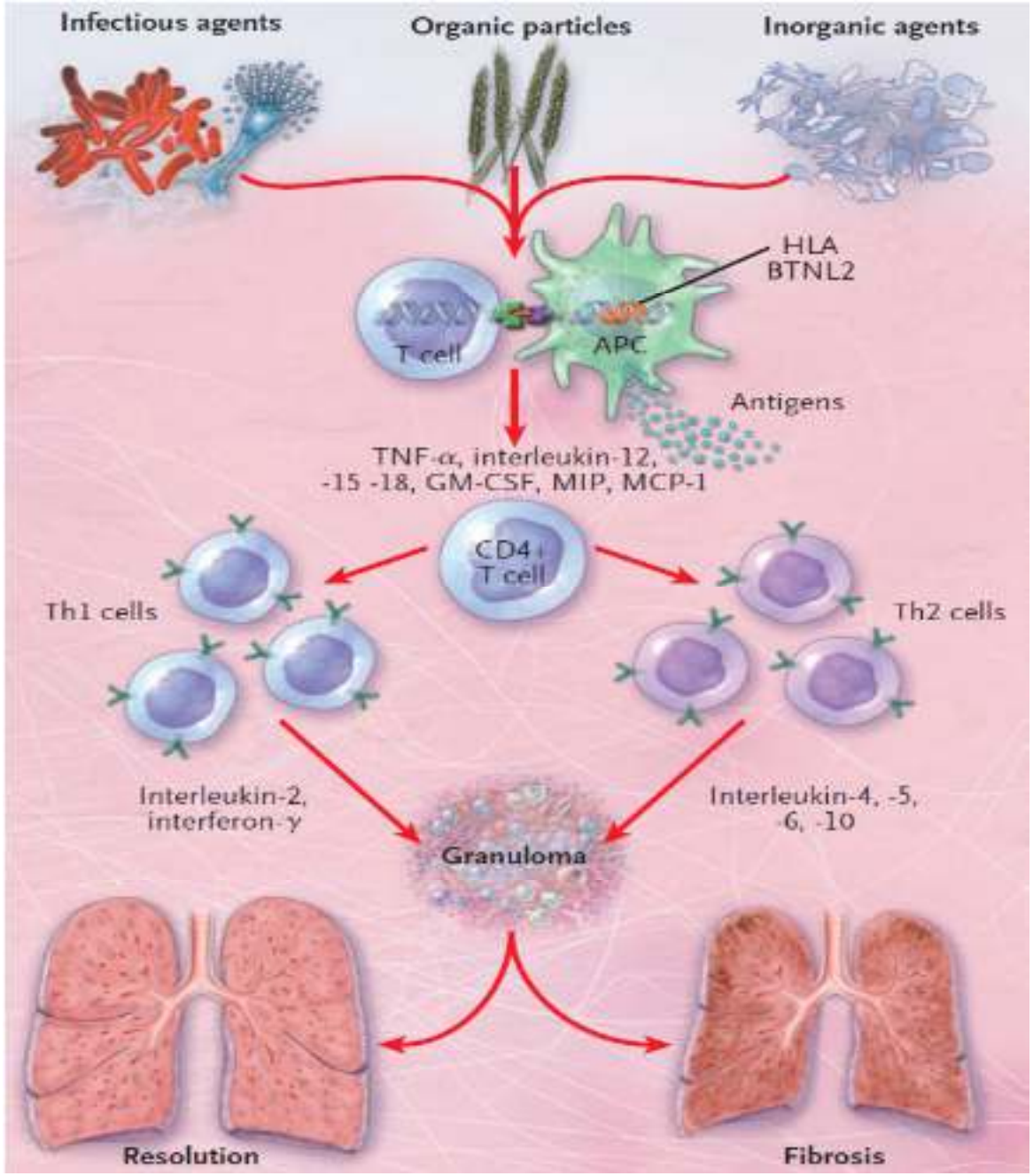
# Genetic Factors

- Familial aggregation, familial linkage, candidate gene, and GWAS
- Studies are challenged by the heterogeneity in presentation and course
  - Reflect differences in underlying genetic susceptibility, environmental triggers, and interaction between two

# Genetic Factors

- Strongest and most consistent region associated with sarcoidosis risk and disease severity risk is the MHC region and HLA-DRB1 variants
- Genes with functional implications: cytokines, cell surface markers, signaling molecules

# Pathogenesis




Baughman et al. *AJRCCM* 2011

# Clinical Approach

# Clinical Approach

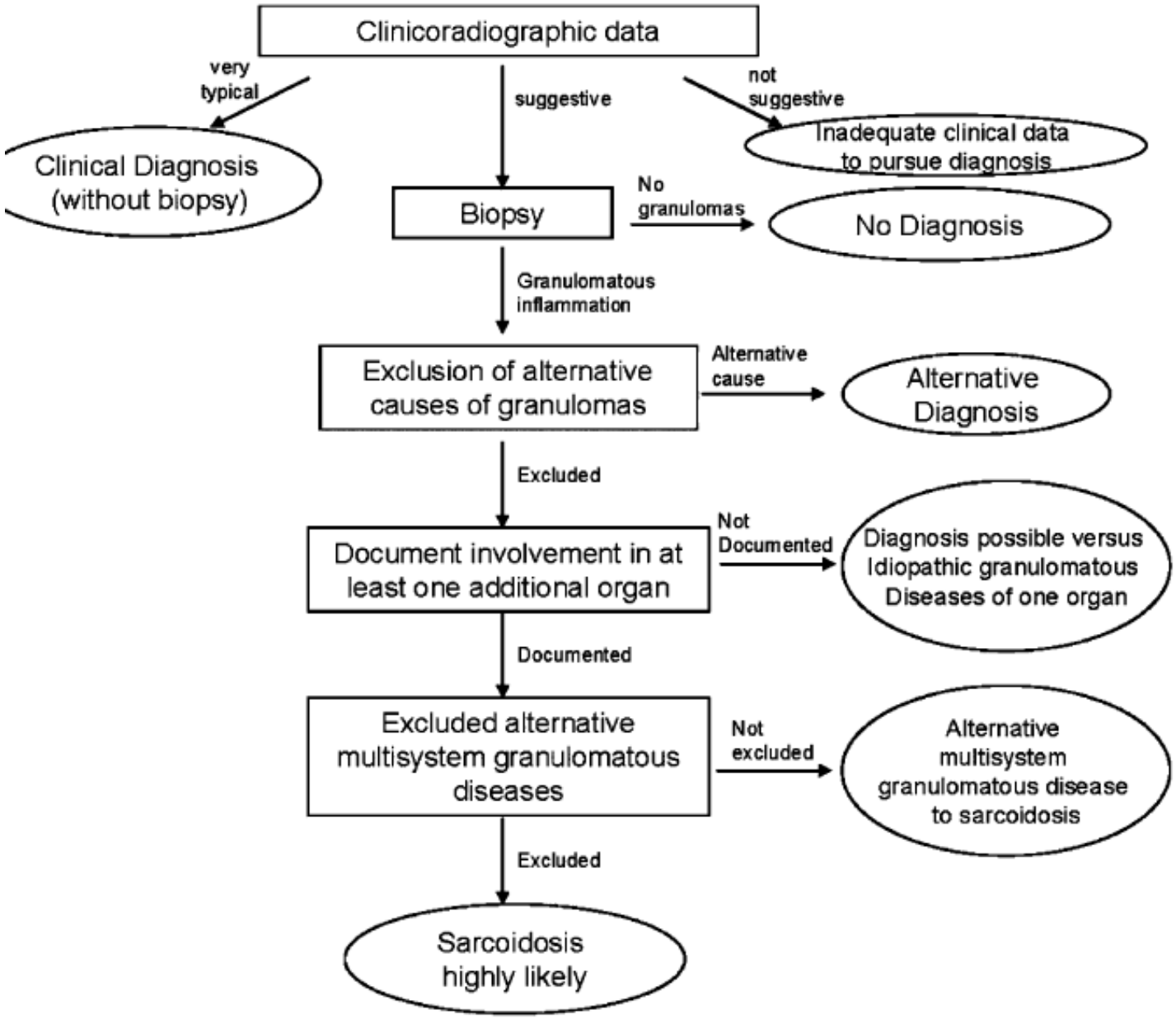
1. Confirm Diagnosis
2. Determine organ involvement
3. Determine need for therapy
   - If therapy needed, decide approach

# Diagnosis

1. Clinical presentation
2. Histopathological confirmation
3. Exclusion of other diseases

*"The presence of one without the other is open to misinterpretation."*
*D Geraint James*

James G. *Sarcoidosis and Other Granulomatous Disorder*, 1985



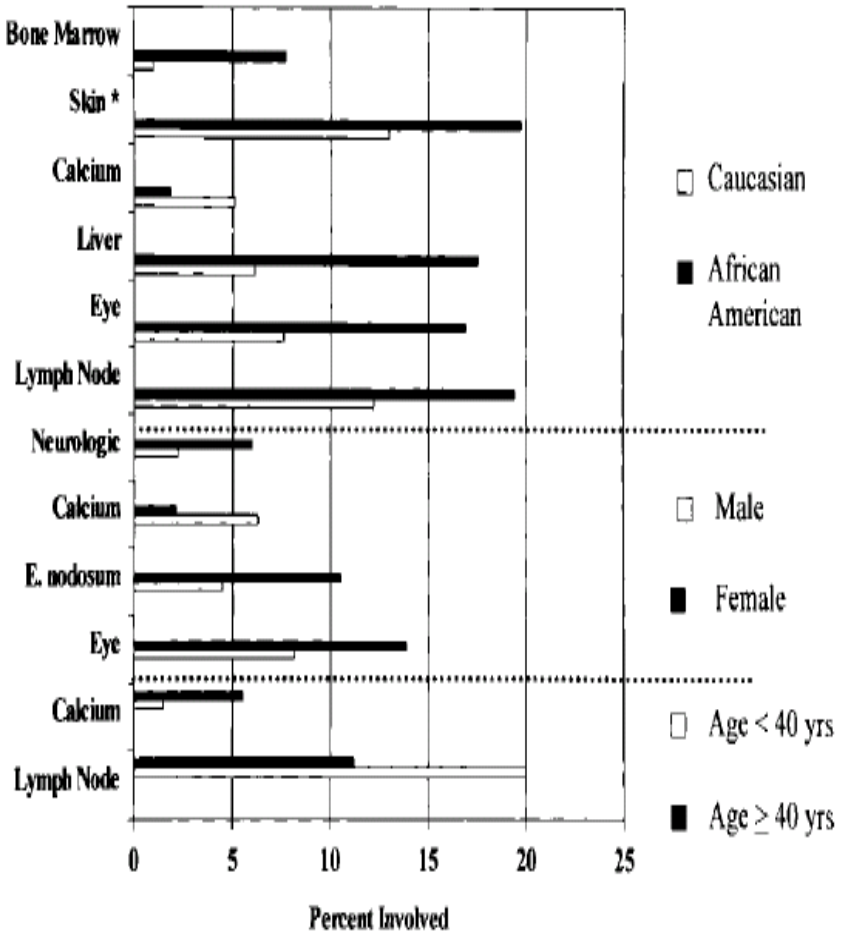

Baughman et al. *AJRCCM* 2011

# Organ involvement

TABLE 1. NUMBER AND PERCENTAGE OF PATIENTS WITH SPECIFIED ORGAN INVOLVEMENT

| Organ Involvement | Number | Percent |
|---|---|---|
| Lungs | 699 | 95.0 |
| Skin* | 117 | 15.9 |
| Lymph node | 112 | 15.2 |
| Eye | 87 | 11.8 |
| Liver | 85 | 11.5 |
| *Erythema nodosum* | 61 | 8.3 |
| Spleen | 49 | 6.7 |
| Neurologic | 34 | 4.6 |
| Parotid/salivary | 29 | 3.9 |
| Bone marrow | 29 | 3.9 |
| Calcium | 27 | 3.7 |
| ENT | 22 | 3.0 |
| Cardiac | 17 | 2.3 |
| Renal | 5 | 0.7 |
| Bone/joint | 4 | 0.5 |
| Muscle | 3 | 0.4 |

*Definition of abbreviation*: ENT = ear, nose, and throat.
* Excluding erythema nodosum.




Baughman et al. *AJRCCM* 2001

# Symptoms and Associated Features

**TABLE 1. Major category of presenting manifestations of sarcoidosis (118 patients)***

| Category | % |
|---|---|
| Respiratory | 25 |
| Constitutional | 24 |
| Asymptomatic | 19 |
| Joint disease | 14 |
| Uveitis | 7 |
| Hepatosplenomegaly | 4 |
| Skin | 3 |
| Other | 4 |
| Total | 100 |

*From reference 19.

**TABLE 2. Associated features at time of histologic diagnosis (118 patients)***

| Feature | % |
|---|---|
| Hilar adenopathy | 79 |
| Peripheral adenopathy | 66 |
| Pulmonary infiltrates | 55 |
| Fever | 31 |
| Skin | 30 |
| Uveitis | 22 |
| Erythema nodosum | 14 |
| Muscle disease | 3 |

*Overlapping features (more than 1 feature for individual patients); from reference 19.

Johns C et al. *Medicine* 1999

# Physical Exam: The Footprints of Sarcoidosis

- Useful findings:
  - Lupus Pernio
  - Uveitis
  - Bilateral facial nerve palsy
  - Lesions along old scars and tattoos
- Uncommon findings:
  - Clubbing (found in 3-6%)
  - Crackles  (found in <2% without fibrosis)
  - Weight loss >10% body weight

Bouvry et al. *Eur Respir J* 2013
Nardi et al. *Eur Respir* J 2011
Yancey et al. *JAMA* 1972

# Serum Angiotensin-Converting Enzyme

- Increased in 60% with acute sarcoidosis
- Increased 10% with chronic sarcoidosis
- In isolation not specific or sensitive enough for diagnosis

**Table 4**
**SACE in diseases other than sarcoidosis**

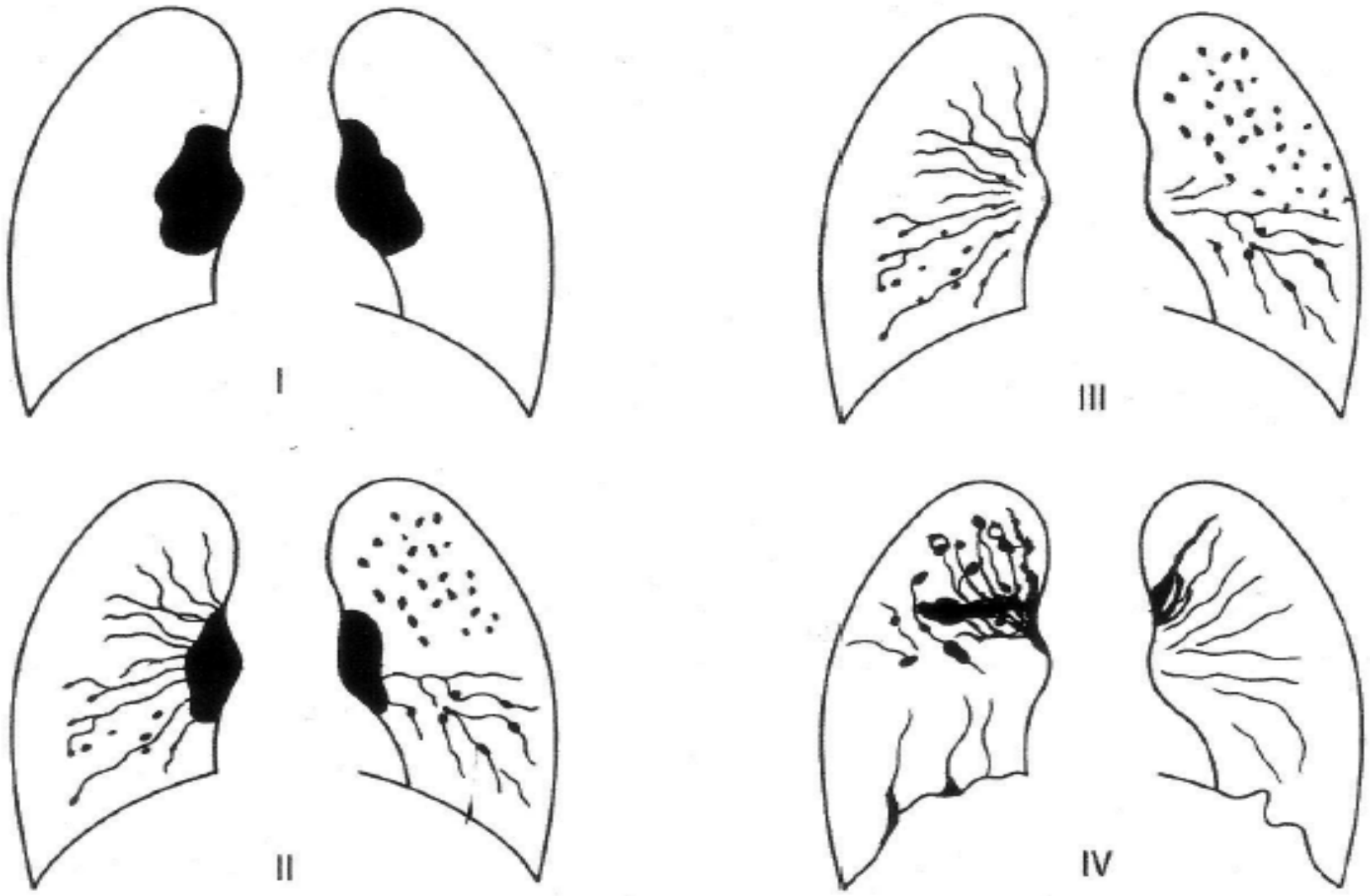
| Disease | N | No. (%) of Measurements >2 SD of Controls, n (%) |
|---|---|---|
| SACE in diseases that may confused with sarcoidosis | | |
| Miliary tuberculosis | 9 | 8 (89) |
| Silicosis | 65 | 30 (45) |
| Primary biliary cirrhosis | 55 | 11 (20) |
| Asbestosis | 32 | 6 (19) |
| Leprosy | 111 | 21 (18) |
| Histoplasmosis | 50 | 7 (14) |
| Atypical mycobacteria | 39 | 5 (13) |
| Berylliosis | 25 | 3 (12) |
| Treated tuberculosis | 132 | 13 (10) |
| Coccidioidomycosis | 18 | 1 (6) |
| Hodgkin's disease | 108 | 7 (6) |
| Lung fibrosis | 161 | 9 (5) |
| Active tuberculosis | 388 | 15 (4) |
| Extrinsic allergic alveolitis | 67 | 3 (4) |
| Lung cancer | 374 | 2 (<1) |
| SACE in other conditions | | |
| Gaucher's disease | 22 | 19 (80) |
| Hyperthyroidism | 87 | 51 (61) |
| Alcoholic liver disease | 151 | 43 (28) |
| Diabetes mellitus | 265 | 48 (18) |
| Bronchial asthma | 288 | 4 (1) |
| Bronchitis and emphysema | 374 | 2 (<1) |

Liberman et al. Am J med 1975
Studdy et al Ann Clin Biochem 1989

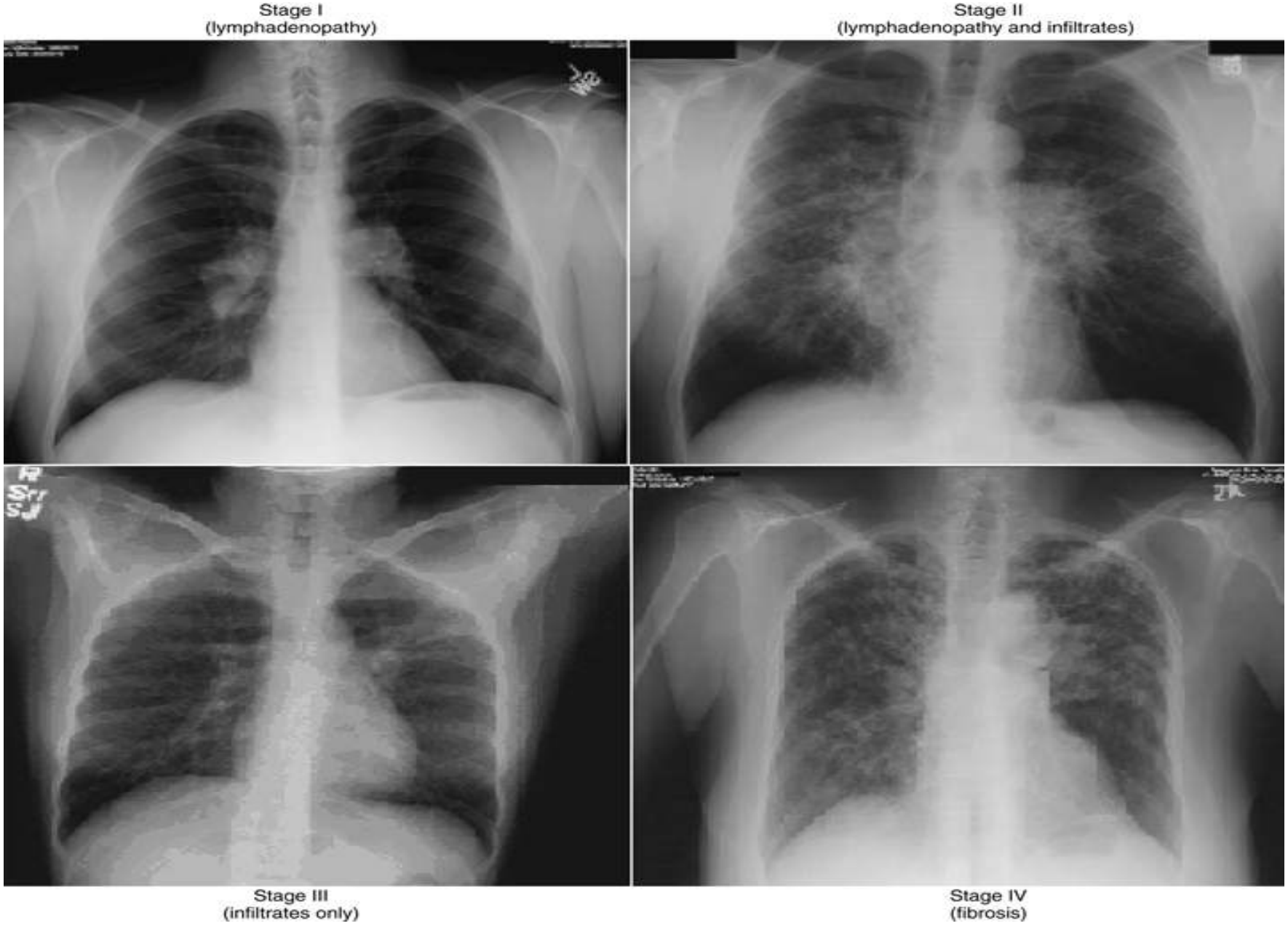
# Other Clinical Clues

- Hypergammaglobulinemia
- Peripheral blood lymphopenia
- Hypercalcemia
- Elevated alkaline phosphatase
- Elevated  1, 25 diOH Vitamin D

# Scadding Stages

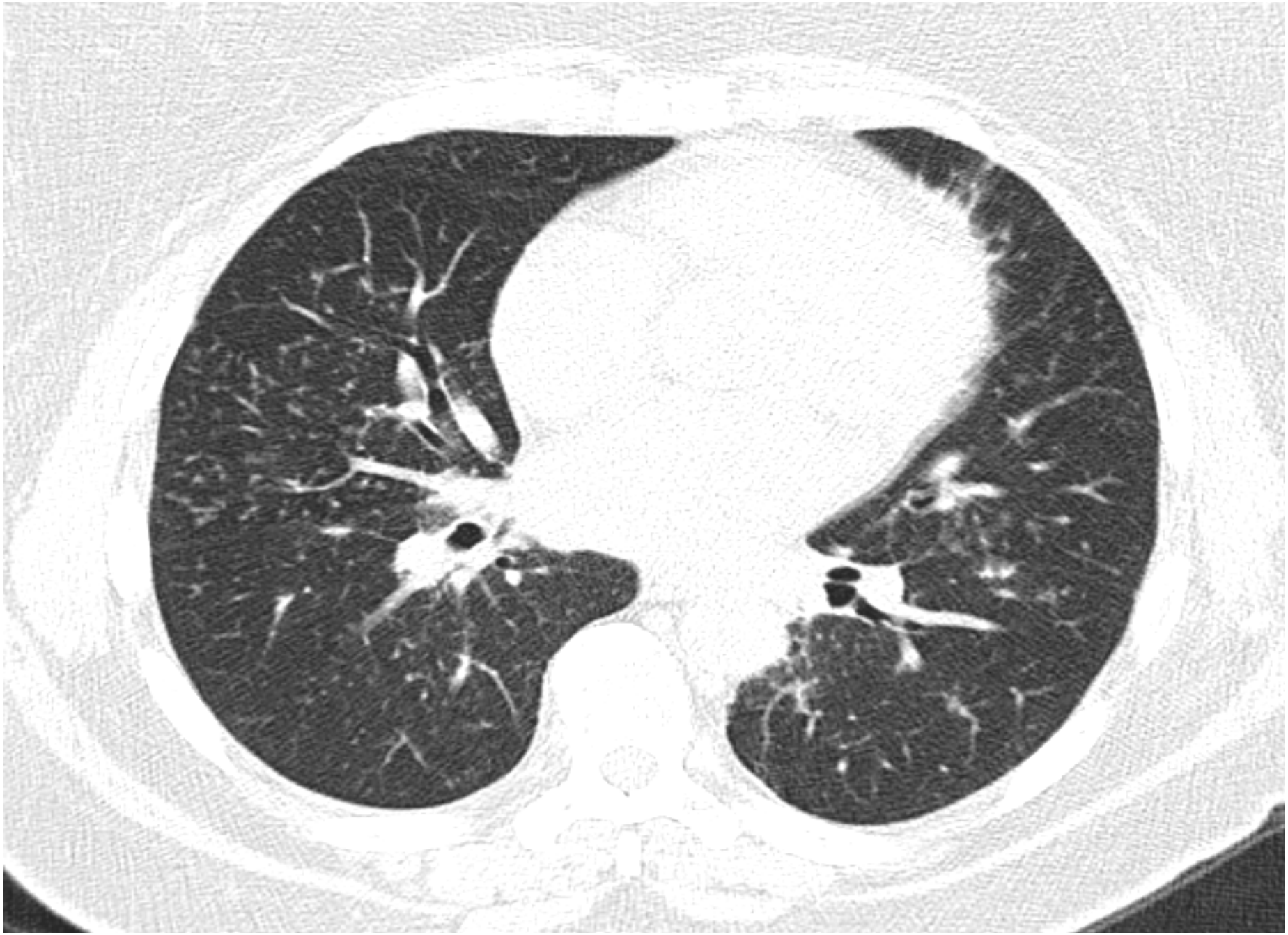


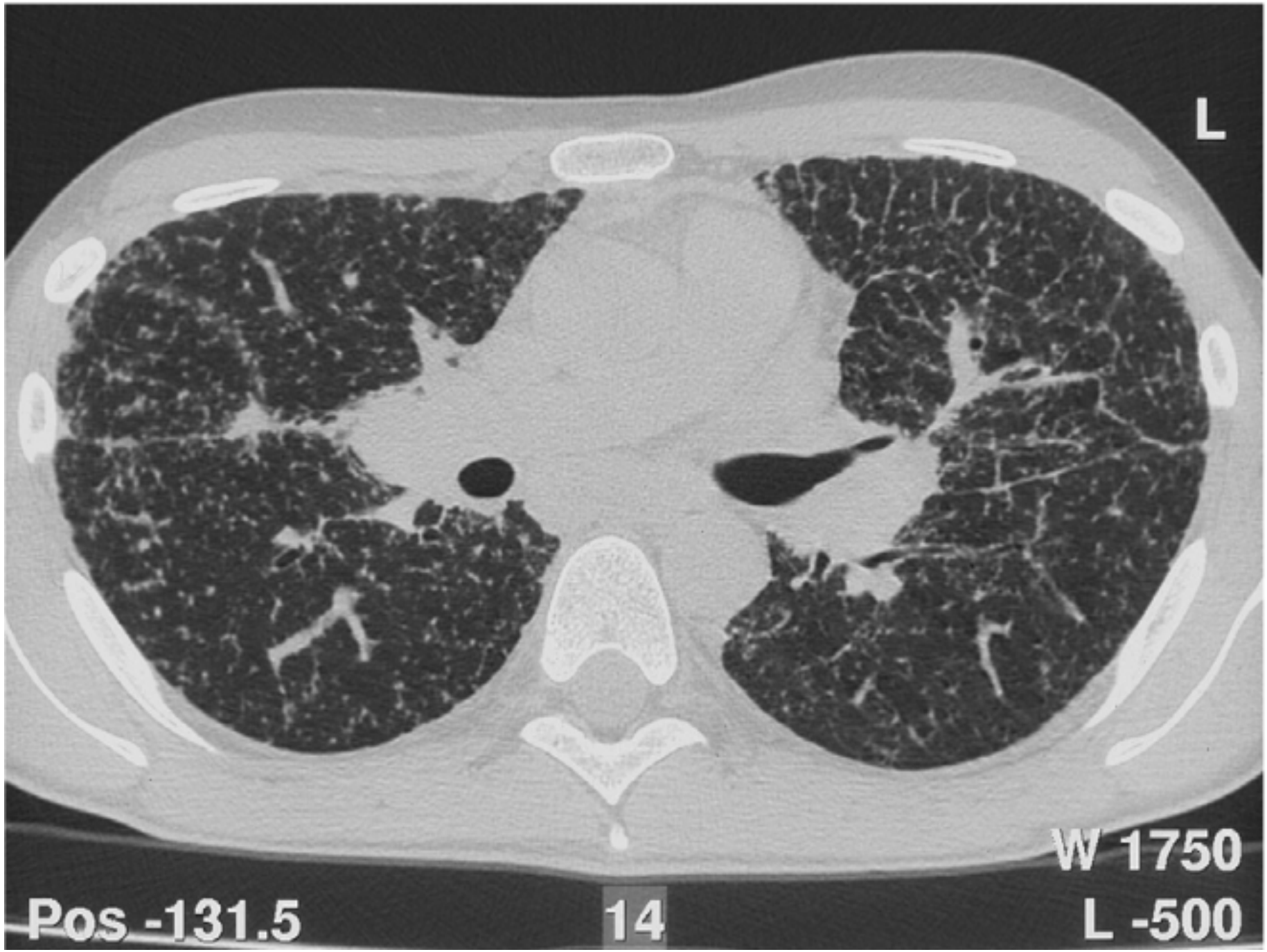
# Scadding Stages



# Classic Findings: Potentially Reversible

- Lymphadenopathy: BL hilar, mediastinal, right paratracheal, subcarinal, aortopulmonary
- Parenchyma: Nodular, Reticulonodular pattern
- Pattern of nodularity following the lymphatics
  - Peribronchovascular bundle
  - Fissures
  - Subpleural region
  - Interlobular septal
- Upper and middle zone parenchymal abnormalities




L
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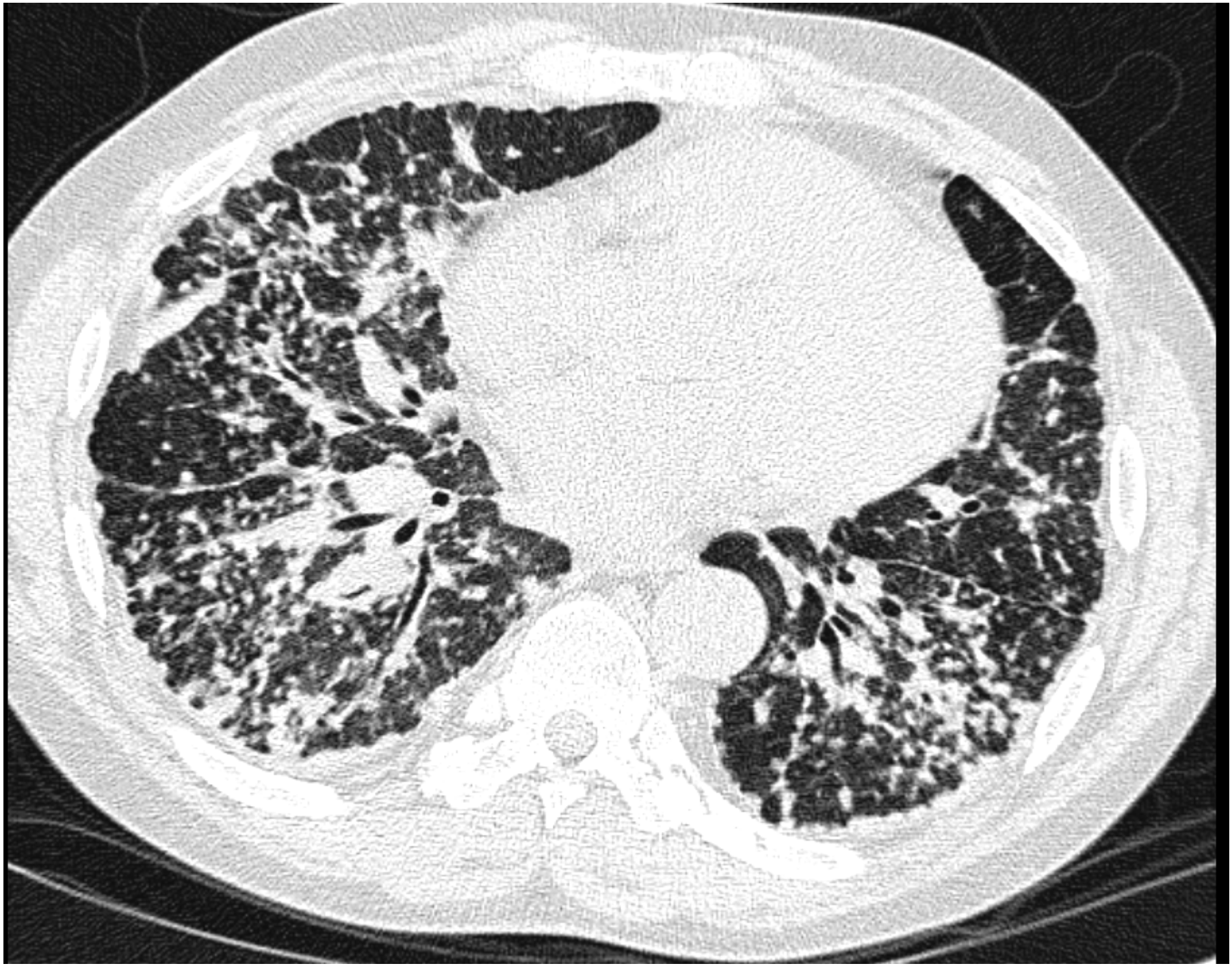
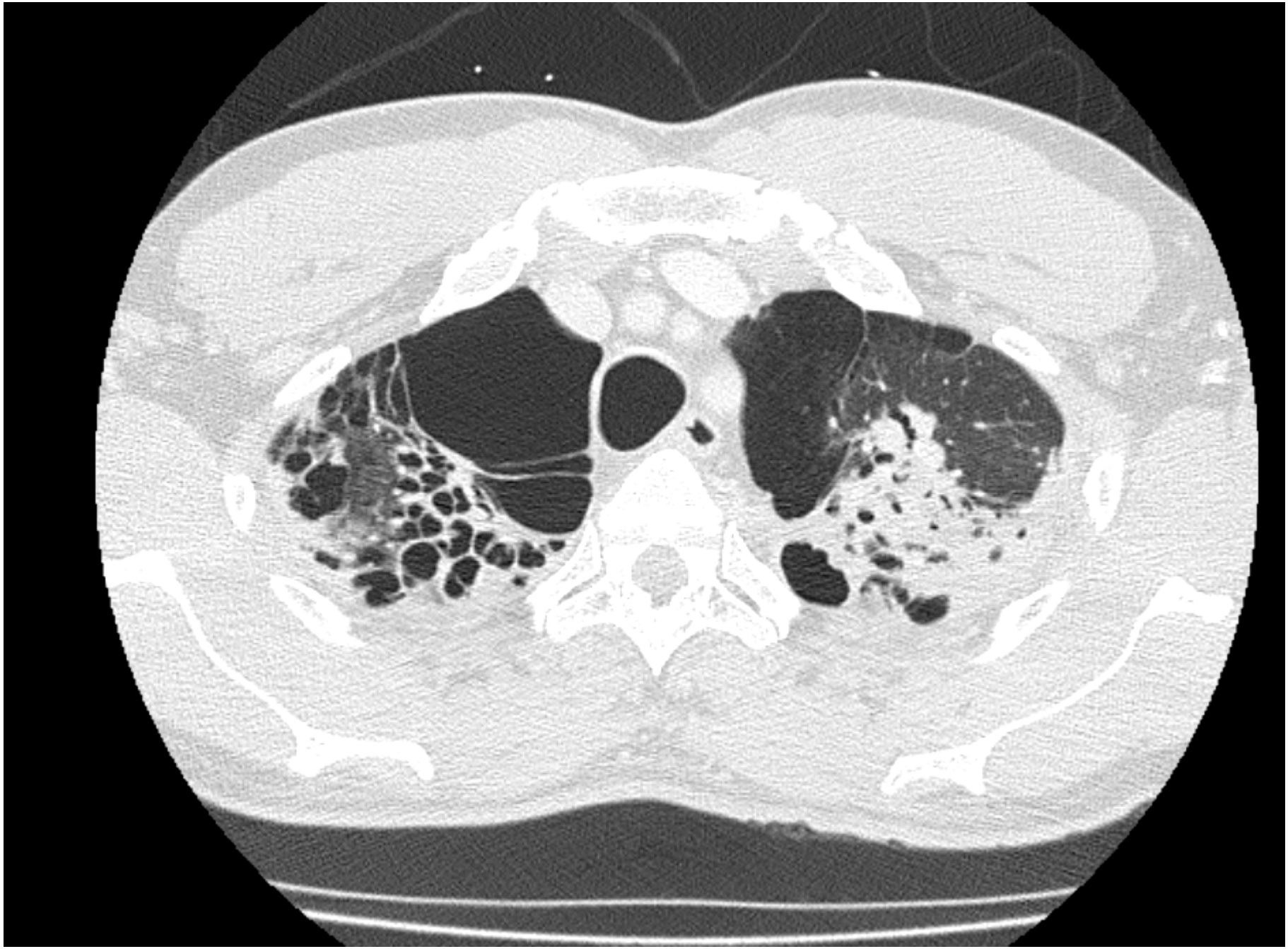
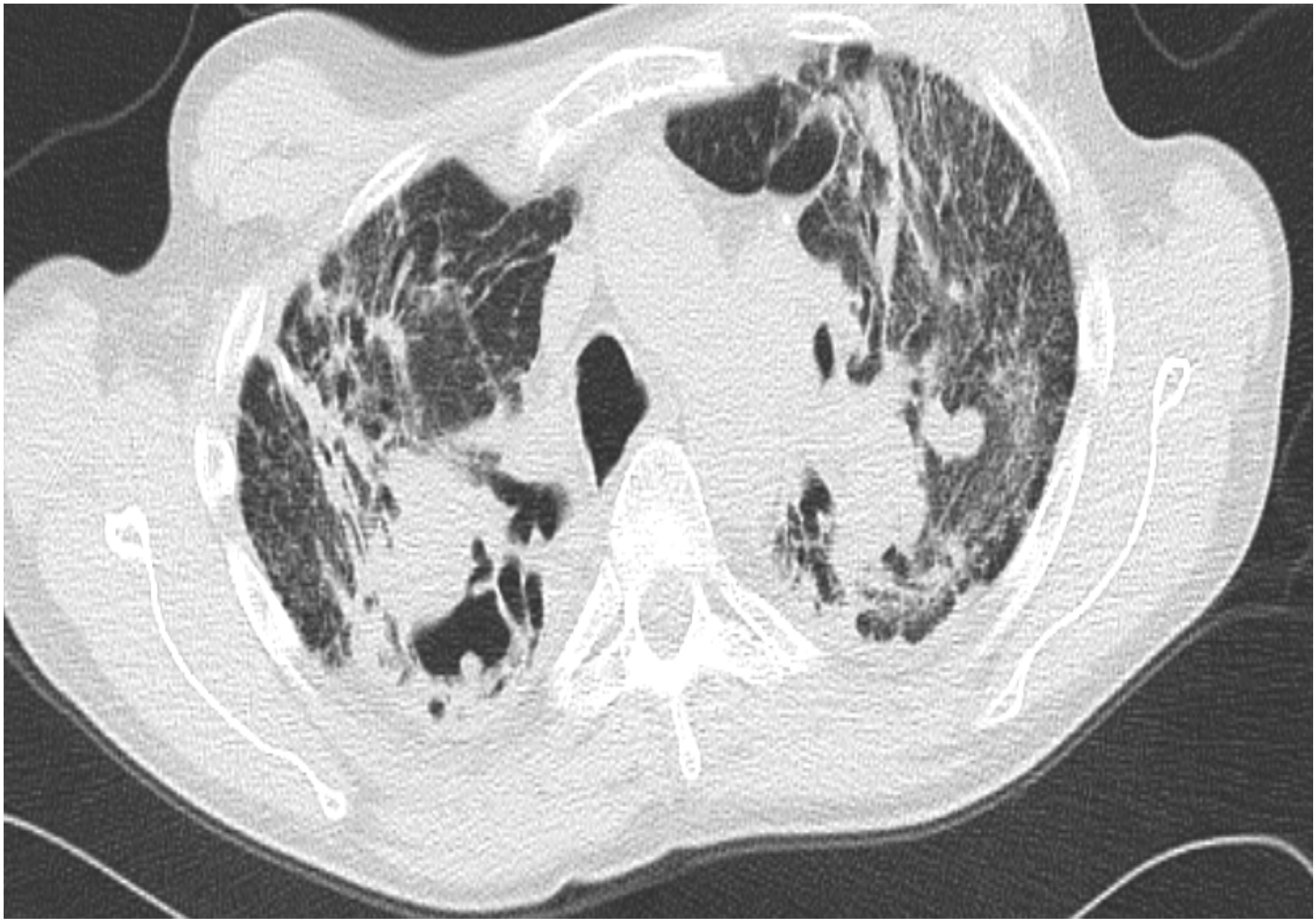
14

# Classic Findings: Irreversible and Chronic Disease

- Reticular opacities: Upper and middle zones
- Architectural distortion
- Traction bronchiectasis
- Volume loss
- Calcified lymph nodes
- Fibrocystic changes



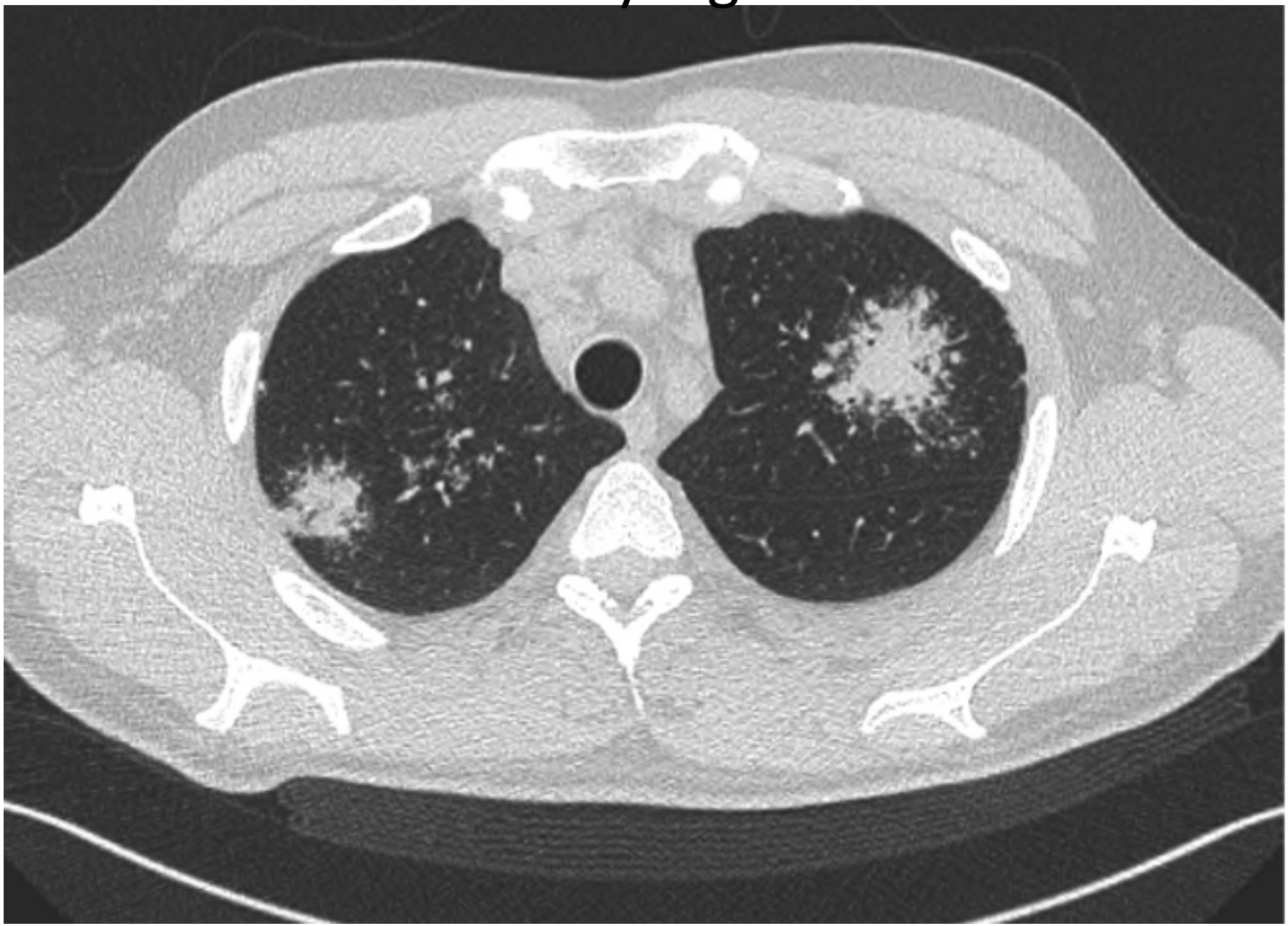




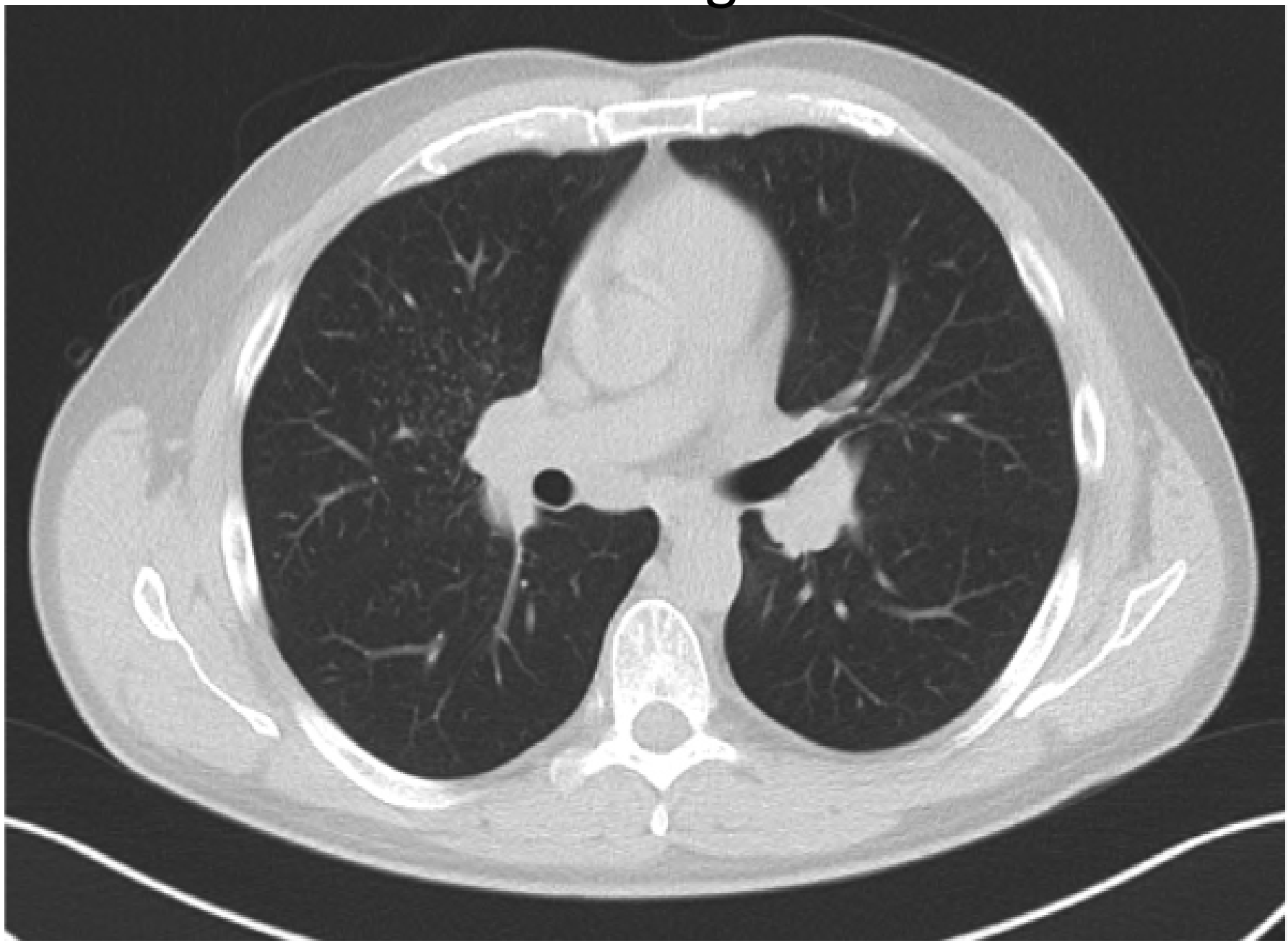
# Uncommon Findings: Potentially Reversible

- Lymphadenopathy: unilateral (more common on R), anterior and posterior mediastinal, paracardiac
- Isolated cavitation
- Isolated GGO without micronodules
- Mosaic attenuation
- Pleural disease
- Mycetoma
- Macronodules: Galaxy sign, cluster sign, reverse halo

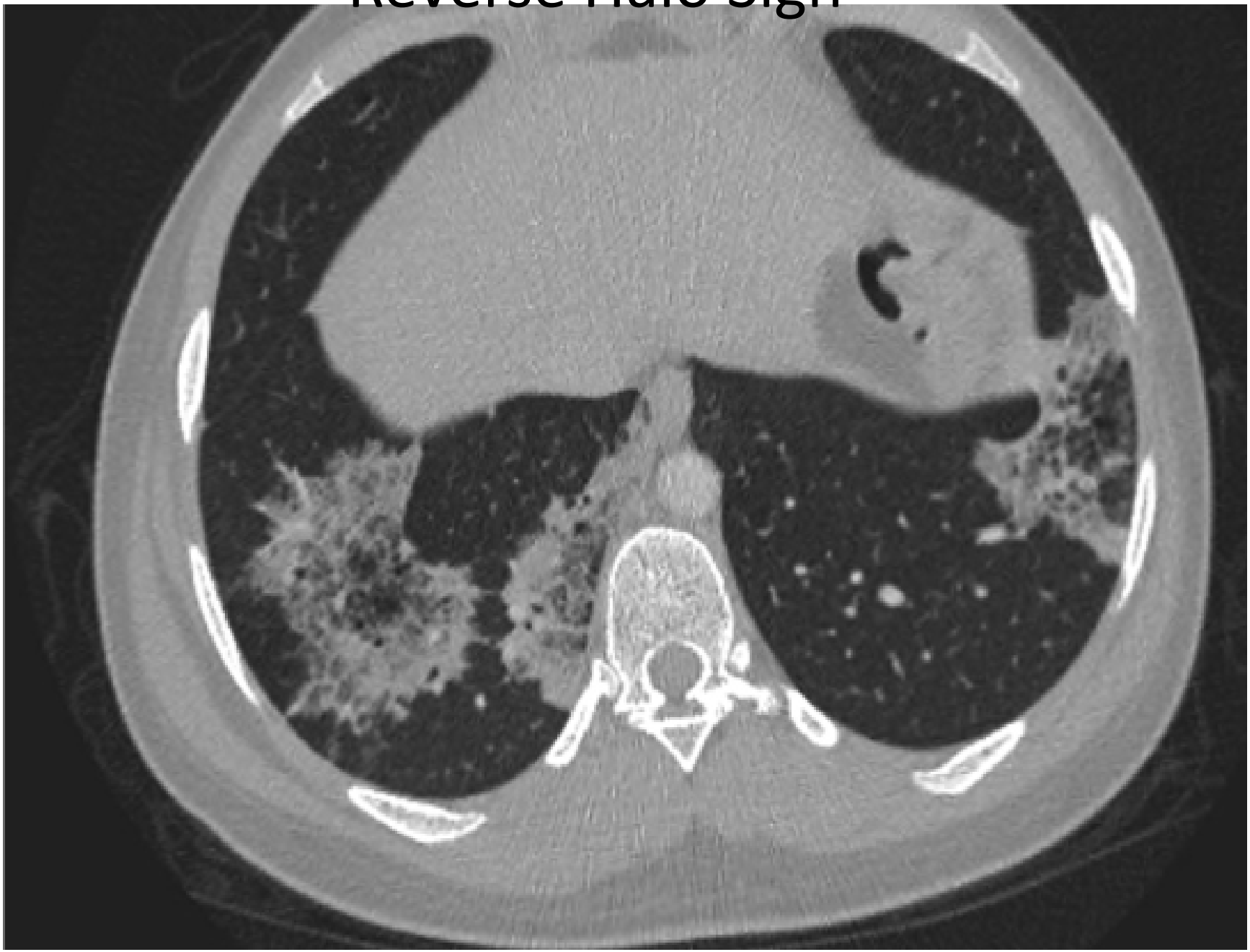
# Galaxy Sign



# Cluster Sign



# Reverse Halo Sign

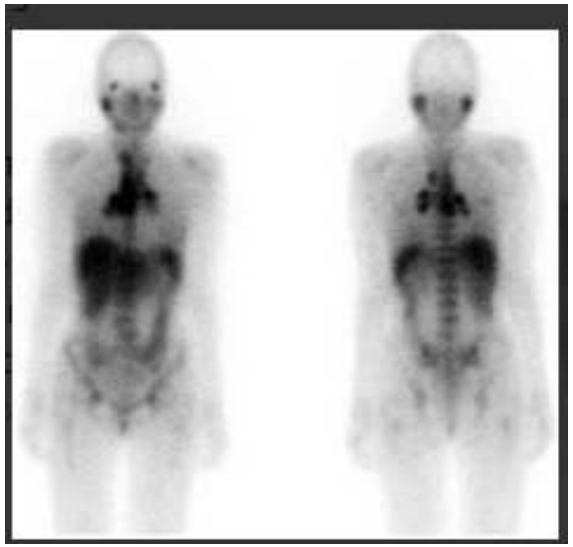


# Biopsies

- Presentation not typical for sarcoidosis, treatment is required, clinical course does not improve/stabilize
  1. Sample easily accessible site
  2. Sample intrathoracic disease

# Situations where biopsy may not be necessary

1. Lofgren Syndrome
   - Bilateral hilar lymphadenopathy
   - Erythema nodosum
   - Arthralgia
   - Fever
2. Heerfordt Syndrome
   - Uveitis
   - Facial paralysis
   - Parotid glands swelling
3. Asymptomatic bilateral hilar adenopathy with right paratracheal LAD and normal physical exam
   - Pretest probability of 99.95%



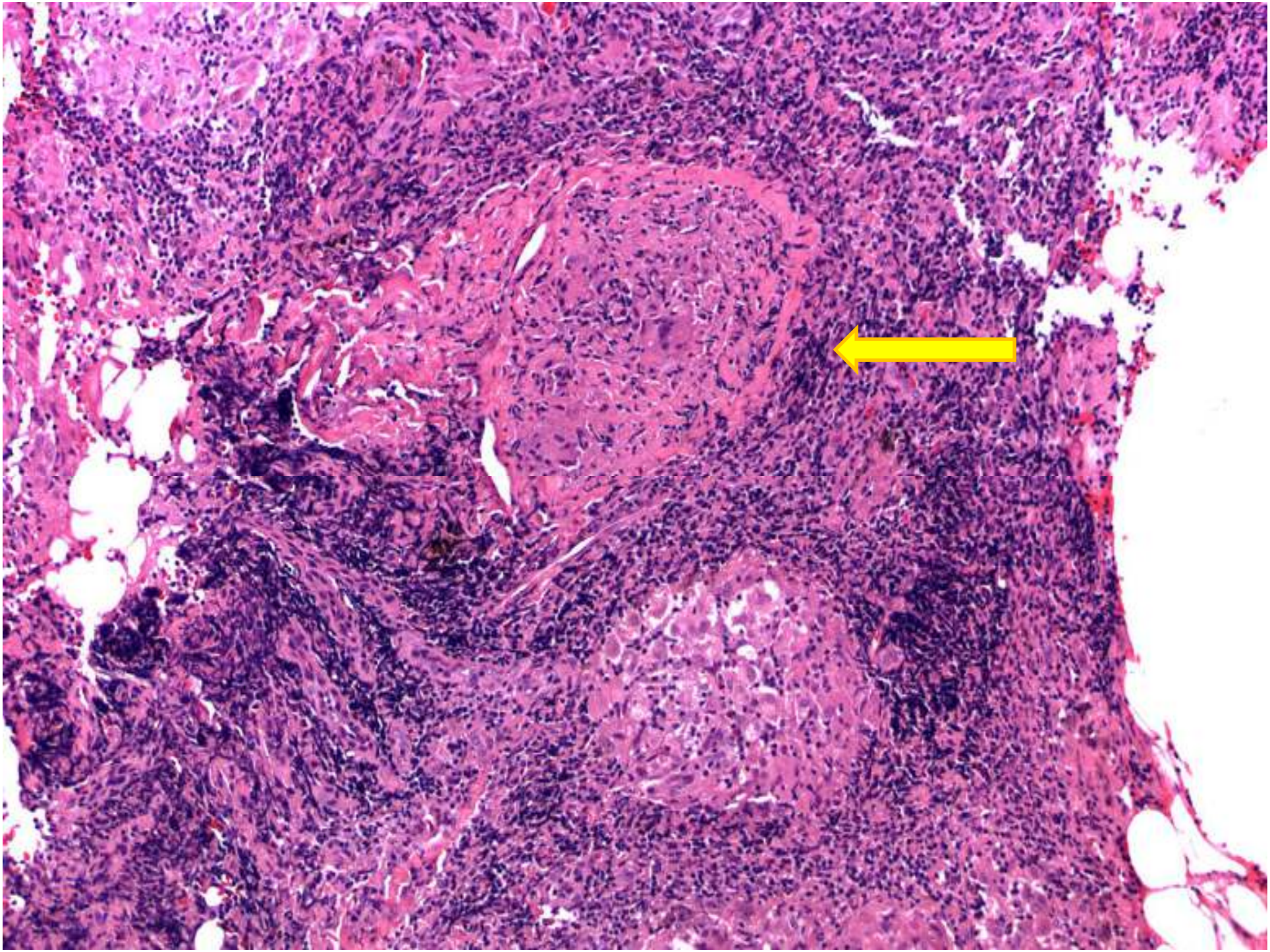
Winterbauer at al. *Ann Intern Med* 1973

# The Granuloma of Sarcoidosis

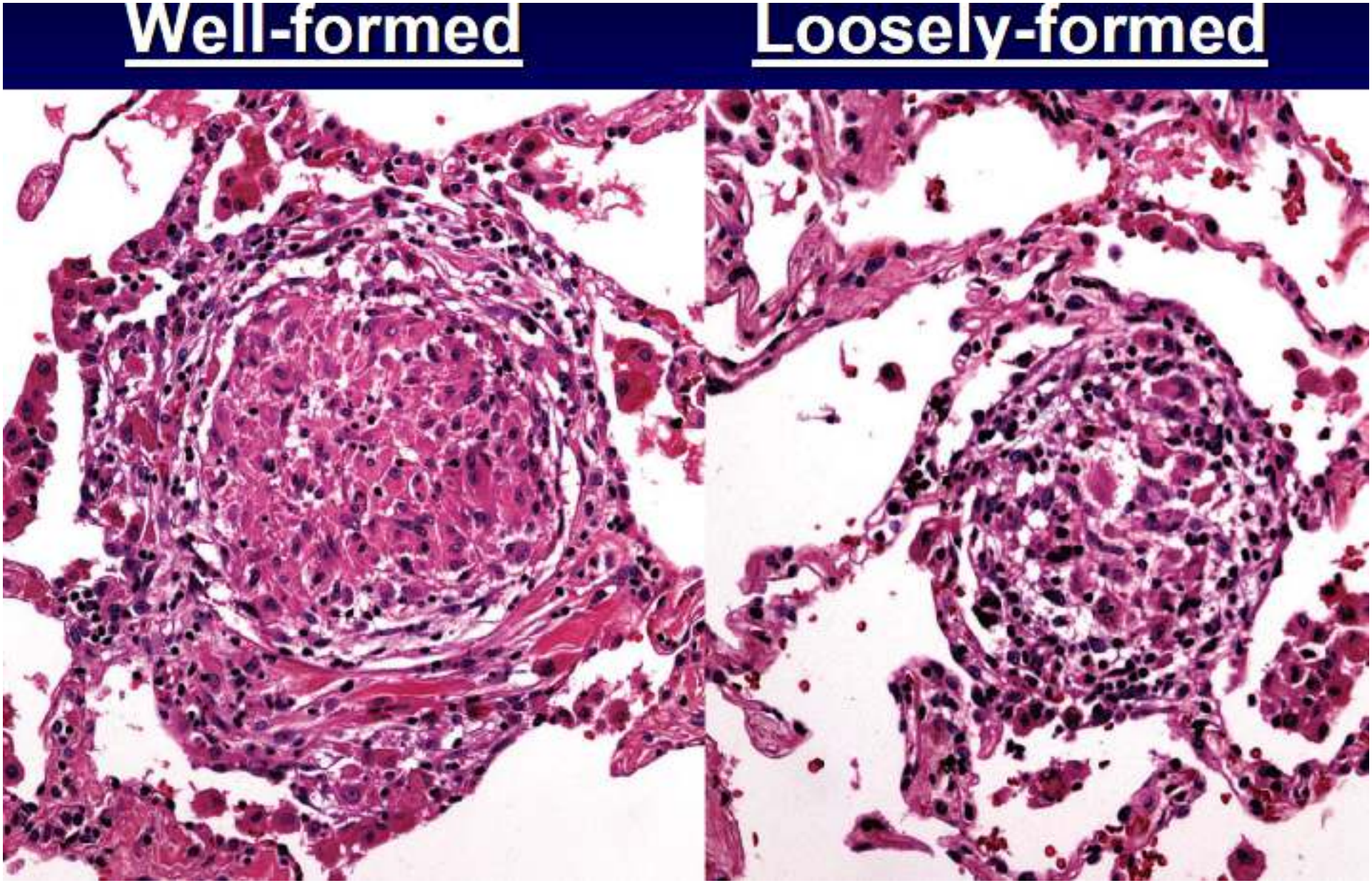
TABLE 1. CLASSIFICATION AND CAUSES OF GRANULOMATOUS DISEASES.

| CAUSE | EXAMPLES OF RESULTING DISEASE | CRITERIA USED TO DIFFERENTIATE THE DISEASE FROM SARCOIDOSIS |
|---|---|---|
| **Infectious agents** | | |
| Mycobacteria | Tuberculosis | Positive culture or stain for acid-fast bacillus |
| | Atypical mycobacterial infection (e.g., due to *Mycobacterium avium* complex, *M. gordonae*, *M. kansasii*) | |
| Fungi | Histoplasmosis | History of possible exposure, culture, presence of urinary antigen for histoplasmosis |
| | Coccidioidomycosis | History of exposure, culture, serologic analyses, skin test |
| Bacteria | Brucellosis | History of exposure, culture, serologic analyses |
| | Chlamydial infection | Serologic analyses, culture |
| | Tularemia | History of possible exposure, serologic analyses |
| Spirochetes | Treponemal infections (e.g., syphilis) | Serologic analyses (e.g., Venereal Disease Research Laboratory test) |
| Parasites | Leishmaniasis | Smear, culture |
| | Toxoplasmosis | Serologic analyses, demonstration of the organism in tissue |
| **Occupational and environmental exposure** | | |
| Organic or inorganic agents | Hypersensitivity pneumonitis (e.g., bacteria, fungi, animal proteins, isocyanates) | History of occupational or environmental exposure, presence of precipitins |
| | Chronic beryllium disease | History of occupational or environmental exposure, beryllium lymphocyte proliferation test of blood or bronchoalveolar-lavage fluid |
| | Granulomatous disease related to other metals (e.g., titanium, aluminum, zirconium) | History of occupational or environmental exposure, analysis of tissue for metals |
| | Talc | Presence of birefringent particles and hypocellular foreign-body granulomas |
| | Methotrexate-induced pneumonitis | History of methotrexate use |
| **Other conditions** | | |
| Neoplasia | Lymphoma | Histologic review of biopsy specimen |
| | Tumor-related granulomas | History of a tumor and spatial association of granulomas with tumor in biopsy specimen |
| Autoimmune disorders | Wegener's granulomatosis | Presence of antineutrophil cytoplasmic antibody, evidence of granulomatous vasculitis or vascular involvement in biopsy specimen |
| | Primary biliary cirrhosis | Presence of antimitochondrial antibodies, prominent biliary involvement |
| | Churg–Strauss syndrome | Presence of peripheral eosinophilia and eosinophilic vasculitis |
| Other | Sarcoidosis | — |

Newman, L et al. *NEJM* 1997



# Two Types of Non-Necrotizing Granulomas




Courtesy of C. Farver

## MAJOR PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF SARCOIDOSIS AT BIOPSY AND SURGICAL PATHOLOGY

| Lung | Lymph Node | Skin | Liver | Bone Marrow | Other Biopsy Sites |
|---|---|---|---|---|---|
| • Tuberculosis<br>• Atypical mycobacteriosis<br>• Cryptococcosis<br>• Aspergillosis<br>• Histoplasmosis<br>• Coccidioidomycosis<br>• Blastomycosis<br>• *Pneumocystis carinii*<br>• *Mycoplasma*, etc.<br>• Hypersensitivity pneumonitis<br>• Pneumoconiosis: beryllium (chronic beryllium disease), titanium, aluminum<br>• Drug reactions<br>• Aspiration of foreign materials<br>• Wegener's granulomatosis (sarcoid-type granulomas are rare)<br>• Chronic interstitial pneumonia, such as usual and lymphocytic interstitial pneumonia<br>• Necrotizing sarcoid granulomatosis (NSG) | • Tuberculosis<br>• Atypical mycobacteriosis<br>• Brucellosis<br>• Toxoplasmosis<br>• Granulomatous histiocytic necrotizing lymphadonitis (Kikuchi's disease)<br>• Cat-scratch disease<br>• Sarcoid reaction in regional lymph nodes to carcinoma<br>• Hodgkin's disease<br>• Non-Hodgkin's lymphomas<br>• Granulomatous lesions of unknown significance (the GLUS syndrome) | • Tuberculosis<br>• Atypical mycobacteriosis<br>• Fungal infection<br>• Reaction to foreign bodies: beryllium zirconium, tattooing, paraffin, etc.<br>• Rheumatoid nodules | • Tuberculosis<br>• Brucellosis<br>• Schistosomiasis<br>• Primary biliary cirrhosis<br>• Crohn's disease<br>• Hodgkin's disease<br>• Non-Hodgkin's lymphomas<br>• GLUS syndrome | • Tuberculosis<br>• Histoplasmosis<br>• Infectious mononucleosis<br>• Cytomegalovirus<br>• Hodgkin's Disease<br>• Non-Hodgkin's lymphomas<br>• Drugs<br>• GLUS syndrome | • Tuberculosis<br>• Brucellosis<br>• Other infections<br>• Crohn's disease<br>• Giant cell myocarditis<br>• GLUS syndrome |

- Sarcoid-like Reaction in malignancy (lymphoma and adenocarcinoma)
- Granulomatous lymphocytic interstitial lung disease (GLILD): [(LIP +/-follicular bronchiolitis)+ granulomas]
- TNF-Alpha antagonist (Infliximab, Etanercept)
- Methotrexate
- Amiodarone
- Sulfasalazine

*AJRCCM* 1999;160:736

Bricker et al. *APMIS* 1991

**Table 1** Incidence of various causes of granulomatous lung disease in lung biopsies and resections

| | No of cases (%) | | |
|---|---|---|---|
| | **USA (n=200)** | **Non-US (n=300)** | **Total (n=500)** |
| **Specific diagnoses** | **133 (67)** | **157 (52)** | **290 (58)** |
| Sarcoidosis | 61 (31) | 75 (25) | 136 (27) |
| Infection | 55 (28) | 70 (23) | 125 (25) |
| Hyersensitivity pneumonitis (EAA) | 11 (6) | 6 (2) | 17 (3.4) |
| Wegener granulomatosis | 2 (1) | 3 (1) | 5 (1.0) |
| Aspiration pneumonia | 2 (1) | 0 (0) | 2 (0.4) |
| Lymphoma or LIP | 1 (0.5) | 1 (0.3) | 2 (0.4) |
| Churg—Strauss syndrome | 0 (0) | 1 (0.3) | 1 (0.2) |
| ANCA-associated disease* | 1 (0.5) | 0 (0) | 1 (0.2) |
| Rheumatoid nodule | 0 (0) | 1 (0.3) | 1 (0.2) |
| **Unknown aetiology** | **67 (33)** | **143 (48)** | **210 (42)** |

Mukhopadhyay et al. *J Clin Pathol* 2012

# Prognosis

- **60-70% spontaneous remission**
- 30-40% chronic or progressive clinical course
- 4-7% severe extra pulmonary involvement
- 1-5% mortality (lungs, heart, CNS) at 5 years

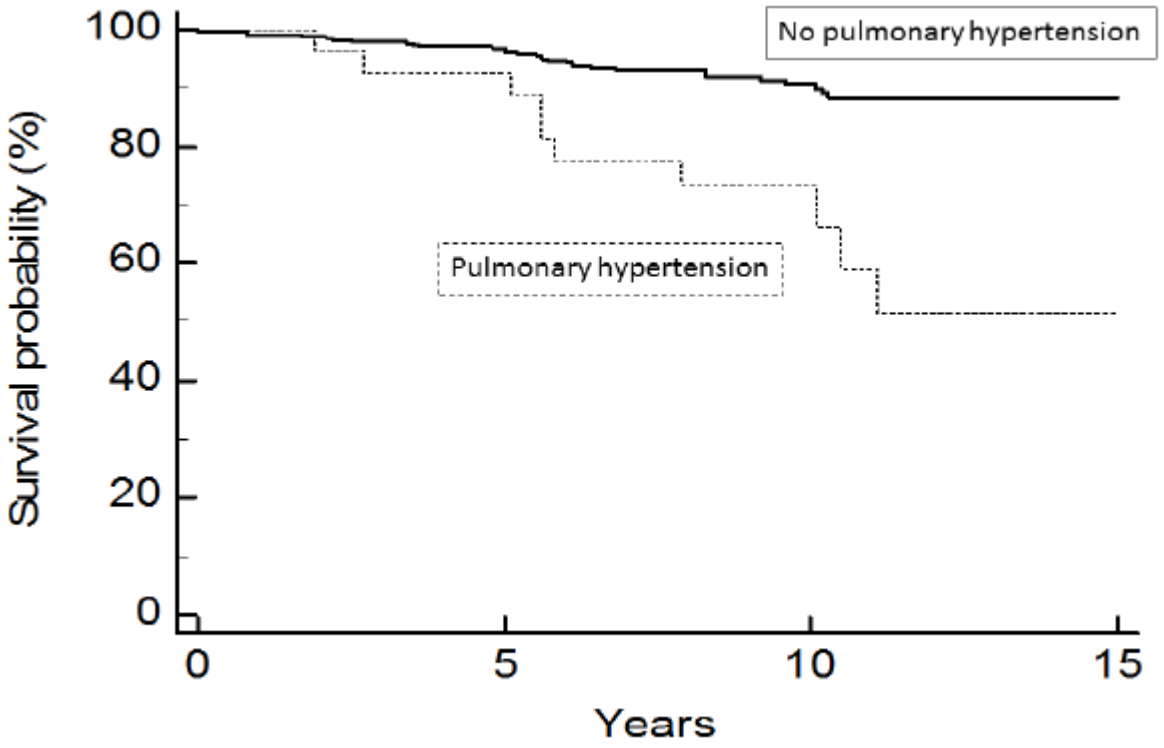
# Poor Prognostic Signs

- Obstruction on spirometry
- Persistent dyspnea
- Pulmonary fibrosis (Scadding Stage IV)
- Neurosarcoidosis
- Lupus pernio
- Heart failure
- Nephrolithiasis
- Bone cysts
- Posterior uveitis

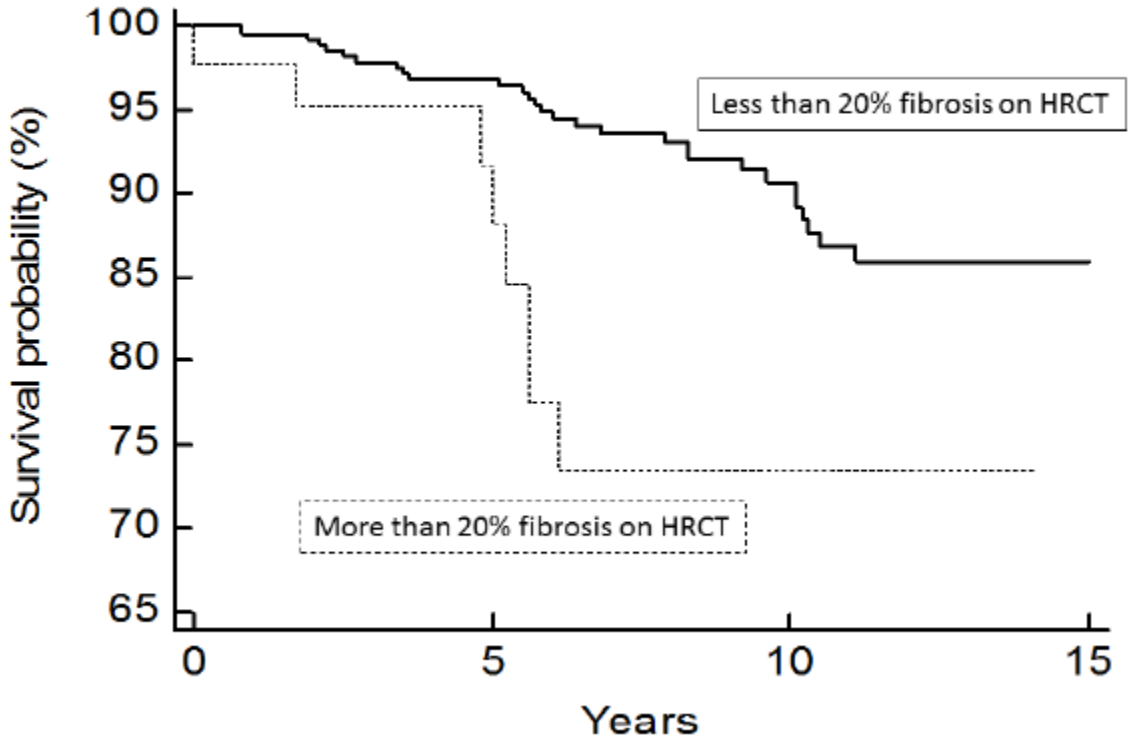
# Prognosis

| Chest X-ray stage * | Number of patients in group | Percent of Total Patients | | Number patients who died from sarcoidosis | Percent of chest x-ray stage who died |
|---|---|---|---|---|---|
| Stage 0 | 47 | 10.4% | | 4 | 8.51% |
| Stage I | 104 | 23.0% | | 2 | 1.92% |
| Stage II | 114 | 25.2% | | 6 | 5.26% |
| Stage III | 109 | 24.1% | | 13 | 11.93% |
| Stage IV | 78 | 17.3% | | 13 | 16.67% |

# Prognosis


No pulmonary hypertension
Pulmonary hypertension
Survival probability (%)
100
80
60
40
20
0
0
5
10
15
Years

# Prognosis


Survival probability (%)
100
95
90
85
80
75
70
65
0
5
10
15
Years
Less than 20% fibrosis on HRCT
More than 20% fibrosis on HRCT

# Walsh score

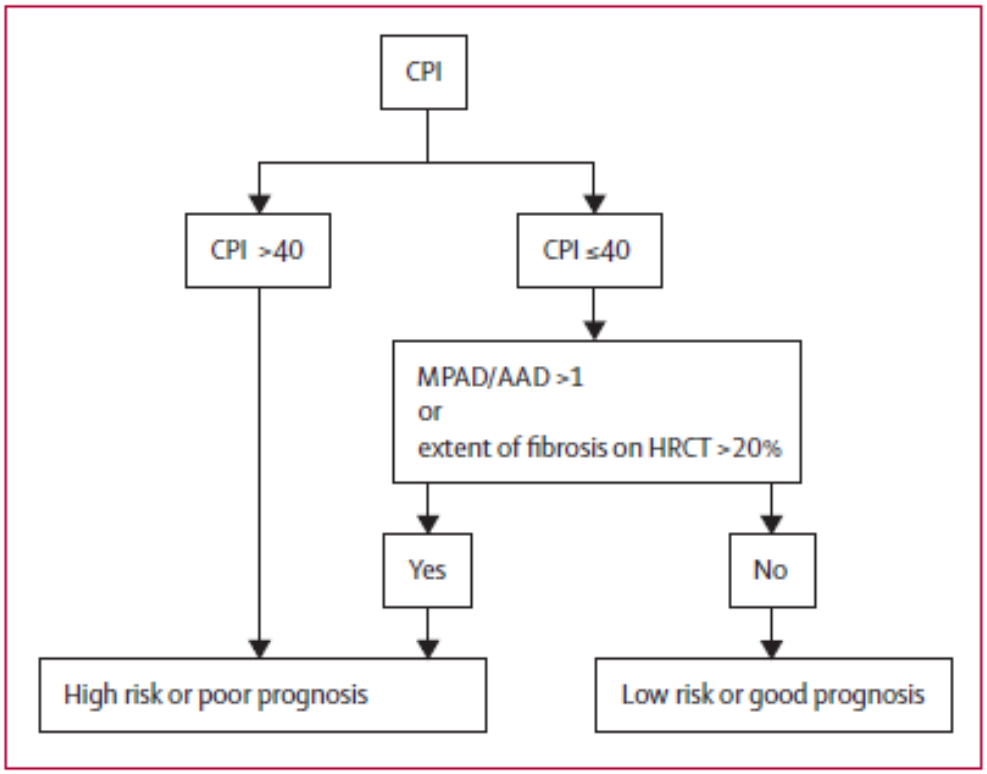
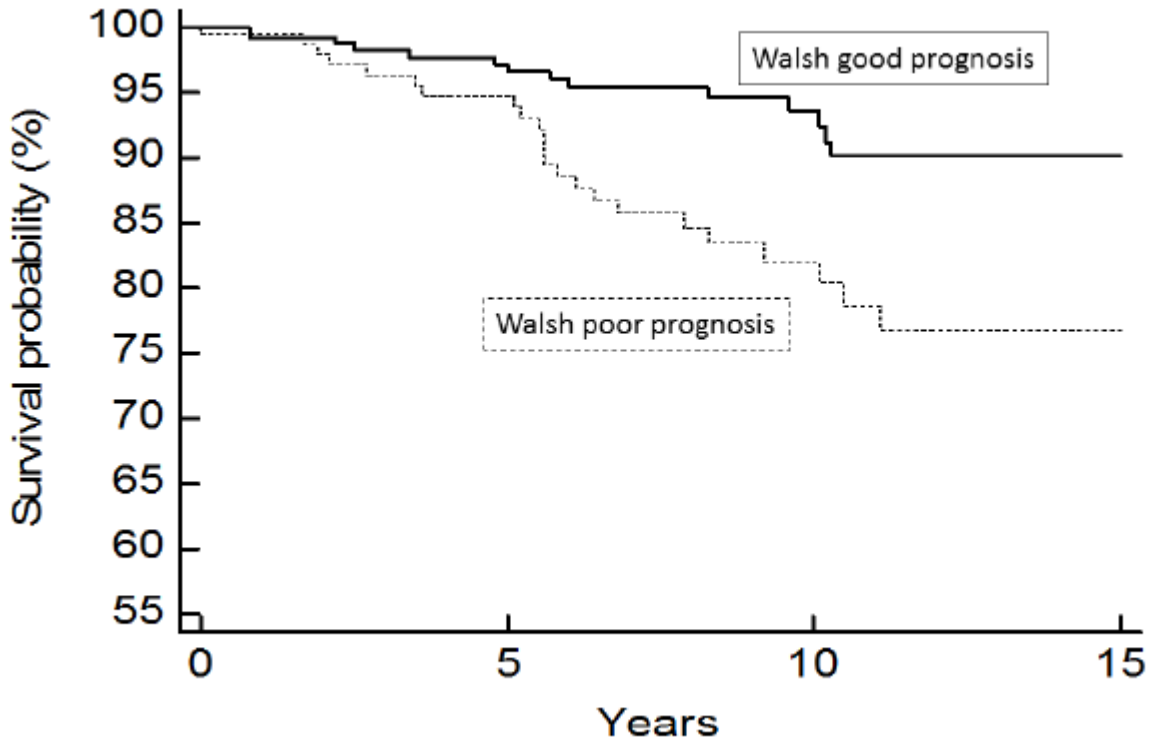



***Figure 1:*** **Clinical staging algorithm for stratification of clinical risk in pulmonary sarcoidosis**

CPI–composite physiological index. HRCT–high-resolution computed tomography. MPAD/AAD–main pulmonary artery diameter to ascending aorta diameter ratio.

# Prognosis


Survival probability (%)
100
95
90
85
80
75
70
65
60
55
0
5
10
15
Years
Walsh good prognosis
Walsh poor prognosis

# Treatment

# Is treatment appropriate?

- What are the symptoms of the sarcoidosis?
  - Sometimes the most bothersome symptoms are not due to sarcoidosis
- How severe are the symptoms (how much is it interfering with my patients life)?
- How severe is the disease on tests (PFTs, Chest xray)?
- Will treatment with medications improve the symptoms?
- Are the risks of treatment worth the benefits?

# Well's Law

**Table 1.** Indications for treating sarcoidosis

Danger
- Organ failure
  - Respiratory
  - Cardiac
  - Neurologic
  - Liver
  - Ocular
- Death

Quality of Life
- Pulmonary
  - Cough
  - Dyspnea
- Eye
  - Visual loss
- Cosmetically important skin lesions
- Calcium dysregulation
- Fatigue
- Small fiber neuropathy

Baughman R. *Sarc Vasc and Diffuse Lung Dis* 2017; 34:280-82

# Major Categories of Medications for Treatment

1. Corticosteroids
2. Cytotoxic Drugs
3. Immune system modifiers and antibodies
4. Other

# Corticosteroids

- Prednisolone, methylprednisolone
- “First line” since rapid response obtained
- Prednisolone is most commonly used at doses of 20-40mg (although higher maybe needed initially in some)
- Broad immunosuppressive activity
- Systematic review
  - Improved symptoms
  - Improved chest xray
  - Improved PFTs 3-24 month

Valeyre D et al. *Semin Respir Crit Care Med* 2017; 38:523-31

# Cytotoxic Drugs

- Methotrexate, leflunomide, azathioprine, mycophenylate, hydroxychloroquin
- Considered “second-line” but maybe started at the same time as corticosteroids
- Limited evidence
- High risk medications but side effects are sometimes better tolerated than those of corticosteroids
- Require close drug monitoring

# TNF- alpha inhibitor

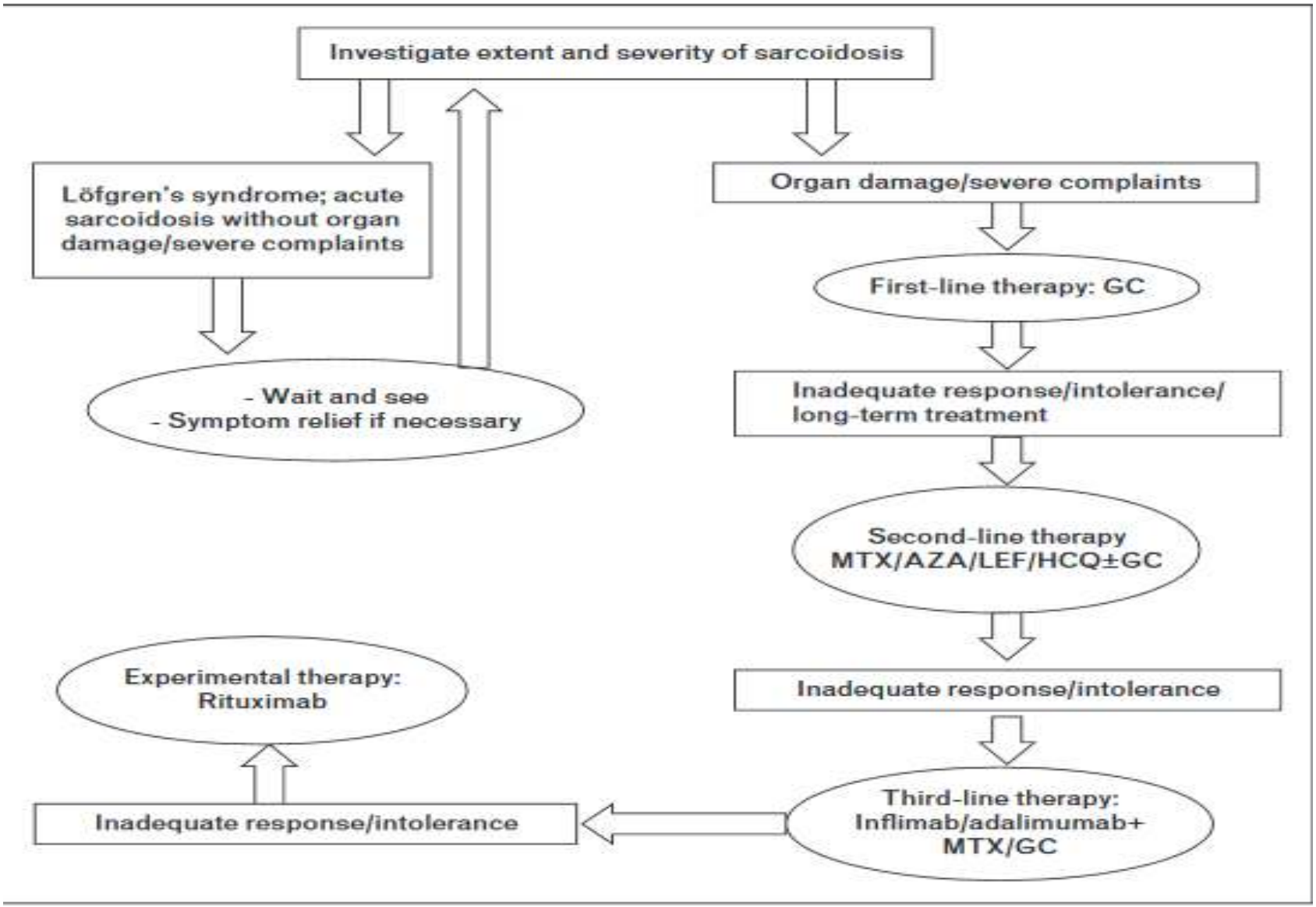
- Infliximab, adalimumab
- “Third line” but maybe used earlier in some situations
- Infliximab is most studied and widely used
- High risk for opportunistic infections
- Risks for use in patients with cardiomyopathy

Wijsenbeek M and Culver D. Clin Chest Med 2015; 36:751-67

# Other therapies

- Repository Corticotropin
- Rituximab
- Cyclophosphamide
- Pentoxifylline
- Thalidomide
- Minocycline

Drake WP et al. *JAMA Dermatol* 2013; 149: 1040-49
Sweiss NJ et al. Eur Resp J 2014; 43:1525-28
Judson MA et al. Eur Resp J 2014; 44:1296-1307




Vorselaars A et al. *Curr Opin Pulm Med* 2014; 20: 479-87

# Supportive Therapies

- Topical medications:
  - Skin, ocular
- Bronchodilators and inhaled steroids
- Oxygen
- Pulmonary rehabilitation
- Physical therapy
- Exercise
- Treatment of sleep apnea
- Treatment of depression

# INTERSTITIAL LUNG DISEASE (ILD)

# Where is the interstitium?

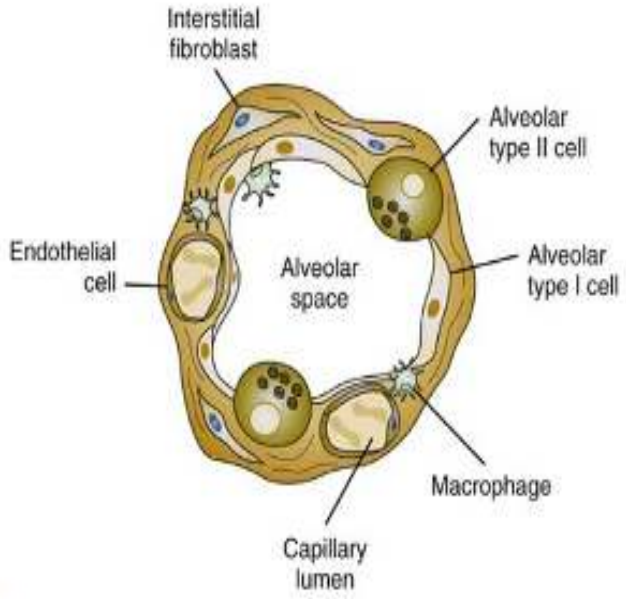



FIGURE 57-1 Schematic depiction of the lung parenchyma surrounding an alveolar sp…

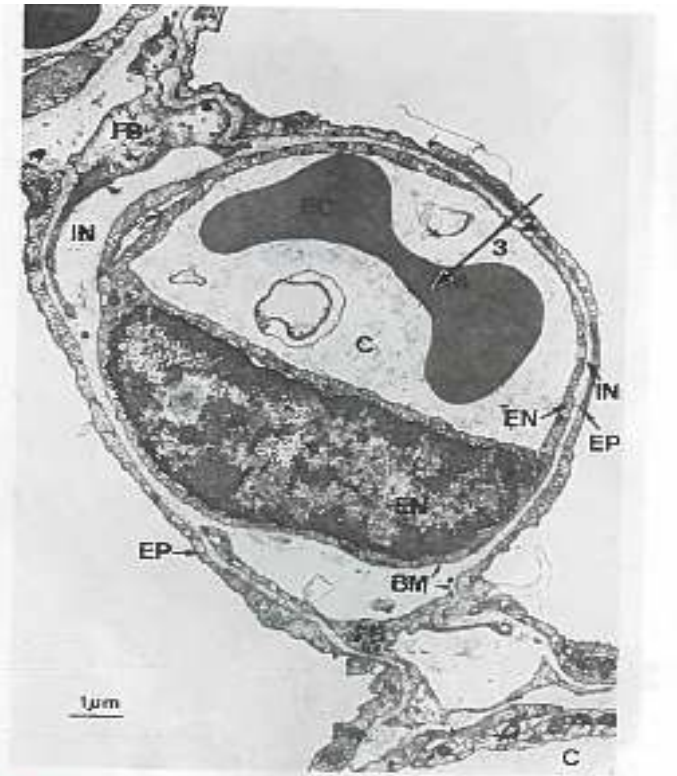



Figure 1-1. Electron micrograph showing a pulmonary capillary (C) in the alveolar wall. Note the extremely thin blood-gas barrier of about 0.3 μm in some places. The large arrow indicates the diffusion path from alveolar gas to the interior of the erythrocyte (EC) and includes the layer of surfactant (not shown in the preparation), alveolar epithelium (EP), interstitium (IN), capillary endothelium (EN), and plasma. Parts of structural cells called fibroblasts (FB), basement membrane (BM), and a nucleus of an endothelial cell are also seen.

# Characteristics

- Histologic hallmark is fibroblastic proliferation and excessive collagen deposition
- “Diffuse parenchymal lung disease” may describe the disease better than “ILD” since the process may start in the interstitium but in most cases invariably involves alternations in alveolar and airway architecture
- ILD can be due to underlying systemic processes or are idiopathic

# Clinical Classifications

**CONNECTIVE TISSUE DISEASES**

- Scleroderma
- Polymyositis-dermatomyositis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease
- Ankylosing spondylitis

**TREATMENT-RELATED OR DRUG-INDUCED DISEASES**

- Antibiotics (nitrofurantoin, sulfasalazine)
- Antiarrhythmics (amiodarone, tocainide, propranolol)
- Anti-inflammatories (gold, penicillamine)
- Anticonvulsants (dilantin)
- Chemotherapeutic agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, chlorambucil, methotrexate, azathioprine, BCNU [carmustine], procarbazine)
- Therapeutic radiation
- Oxygen toxicity
- Narcotics

**OCCUPATIONAL AND ENVIRONMENTAL DISEASES**

**Inorganic**

- Silicosis
- Asbestosis
- Hard-metal pneumoconiosis
- Coal worker's pneumoconiosis
- Berylliosis
- Talc pneumoconiosis
- Siderosis (arc welder)
- Stannosis (tin)

**Organic (hypersensitivity pneumonitis)**

- Bird breeder's lung
- Farmer's lung
- (For complete listing, see Chapter 66 )

**IDIOPATHIC FIBROTIC DISORDERS**

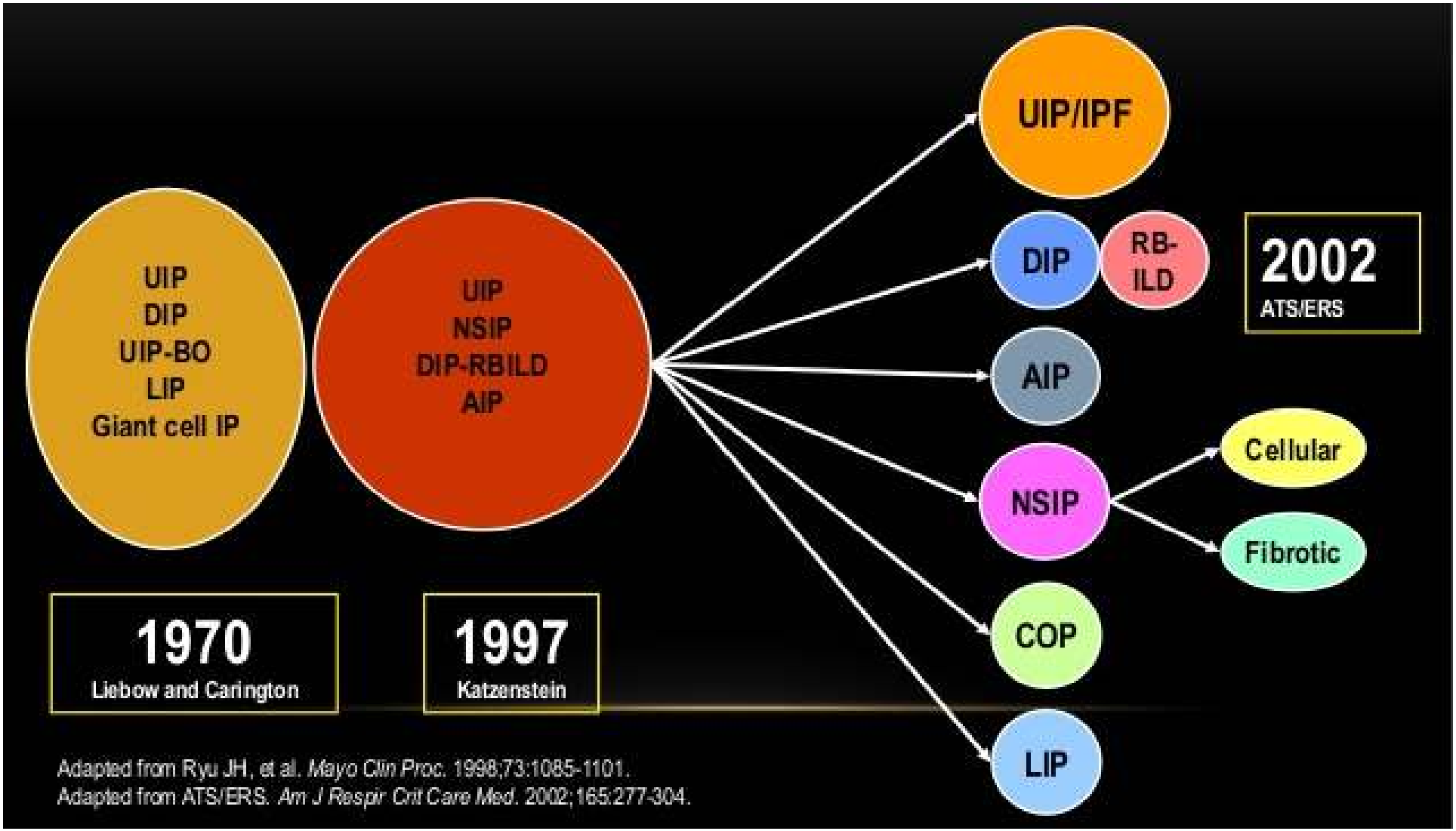
- Acute interstitial pneumonitis (Hamman-Rich syndrome)
- Idiopathic pulmonary fibrosis/usual interstitial pneumonia
- Familial pulmonary fibrosis
- Respiratory bronchiolitis/desquamative interstitial pneumonitis
- Cryptogenic organizing pneumonia
- Nonspecific interstitial pneumonia
- Lymphocytic interstitial pneumonia (Sjögren's syndrome, connective tissue disease, AIDS, Hashimoto's thyroiditis)
- Autoimmune pulmonary fibrosis (inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia)

**PRIMARY (UNCLASSIFIED) DISEASES**

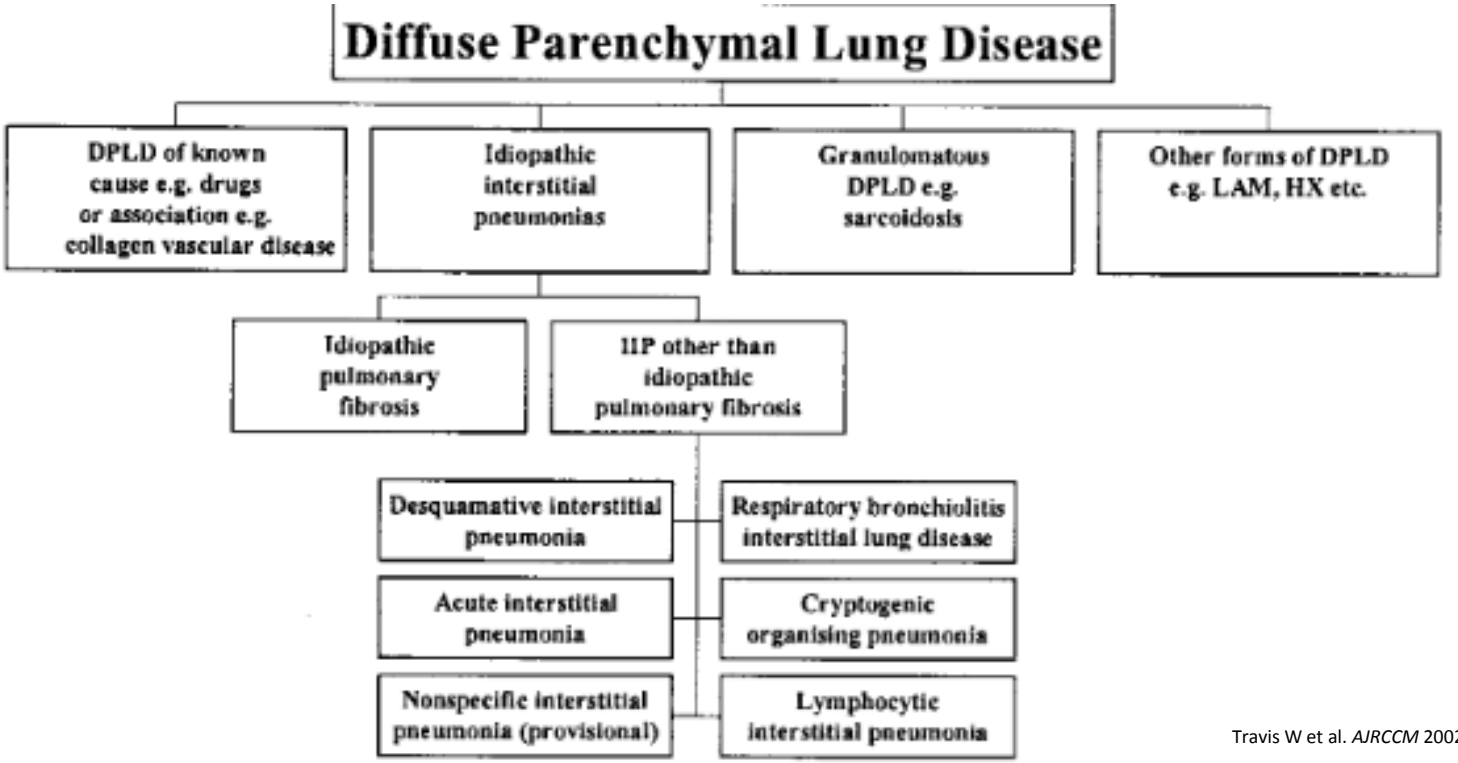
- Sarcoidosis
- Primary pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
- Amyloidosis
- Pulmonary vasculitis
- Lipoid pneumonia
- Lymphangitic carcinomatosis
- Bronchoalveolar carcinoma
- Pulmonary lymphoma
- Gaucher's disease
- Niemann-Pick disease
- Hermansky-Pudlak syndrome
- Neurofibromatosis
- Lymphangioleiomyomatosis
- Tuberous sclerosis
- Acute respiratory distress syndrome
- AIDS
- Bone marrow transplantation
- Postinfectious
- Eosinophilic pneumonia
- Alveolar proteinosis
- Diffuse alveolar hemorrhage syndromes
- Alveolar microlithiasis
- Metastatic calcification

# Incidence

- 31.5/100,000/yr in men
- 26.1/100,000/yr in women
- Rises with age


UIP
DIP
UIP-BO
LIP
Giant cell IP
UIP
NSIP
DIP-RBILD
AIP
1970
Liebow and Carington
1997
Katzenstein
UIP/IPF
DIP
RB-ILD
AIP
NSIP
Cellular
Fibrotic
COP
LIP
2002
ATS/ERS
Adapted from Ryu JH, et al. Mayo Clin Proc. 1998;73:1085-1101.
Adapted from ATS/ERS. Am J Respir Crit Care Med. 2002;165:277-304.

# ATS/ERS 2002 Classification




Travis W et al. *AJRCCM* 2002; 165:277-302

**Known Causes**

- Drug induced
- CTD-ILD

**Idiopathic (IIPs)**

- Sarcoidosis
- COP
- IPF
- NSIP
- DIP
- RBILD
- AIP

**An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias**

## TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias*

Travis W et al. *AJRCCM* 2013; 188:733-48

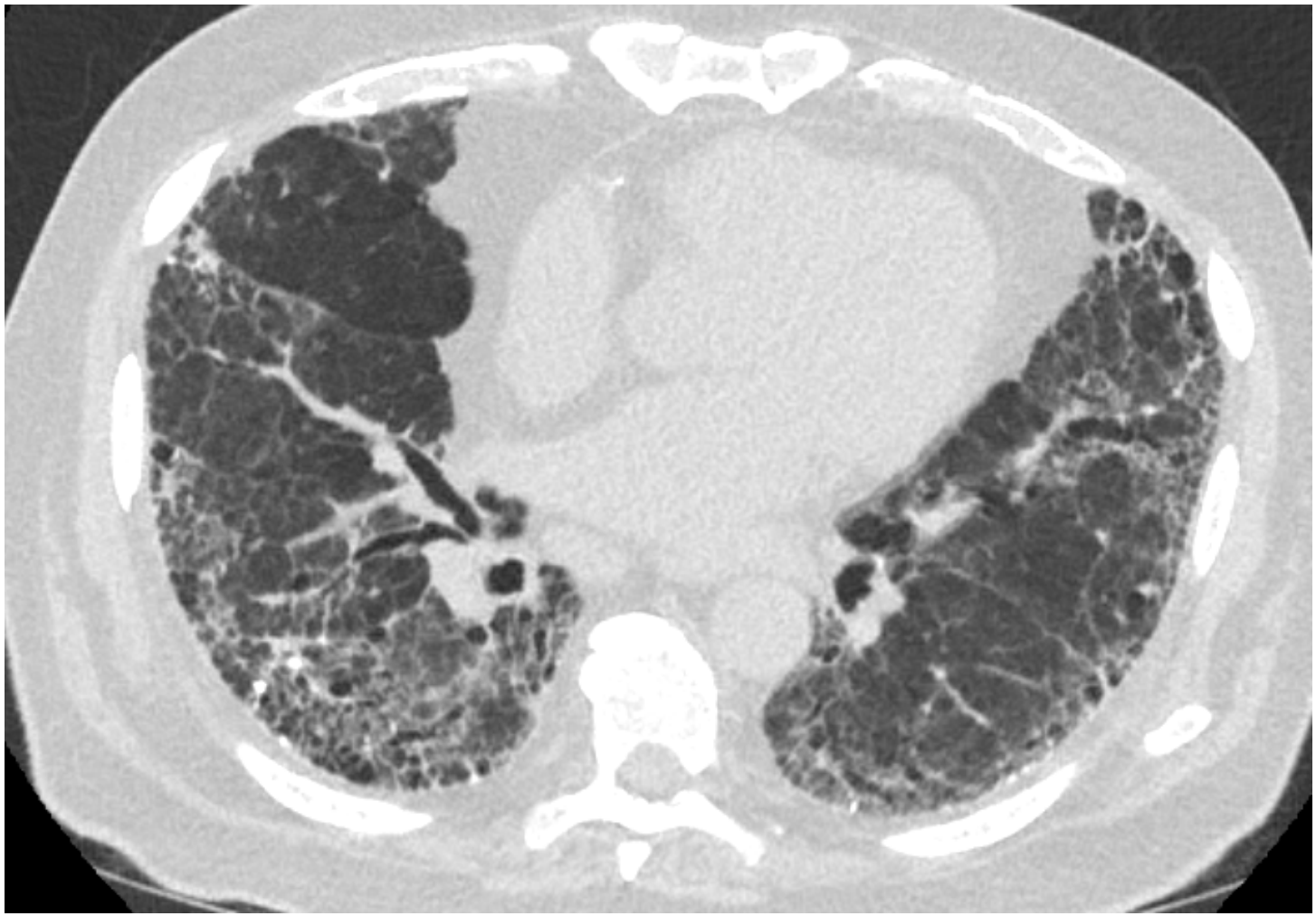
## TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

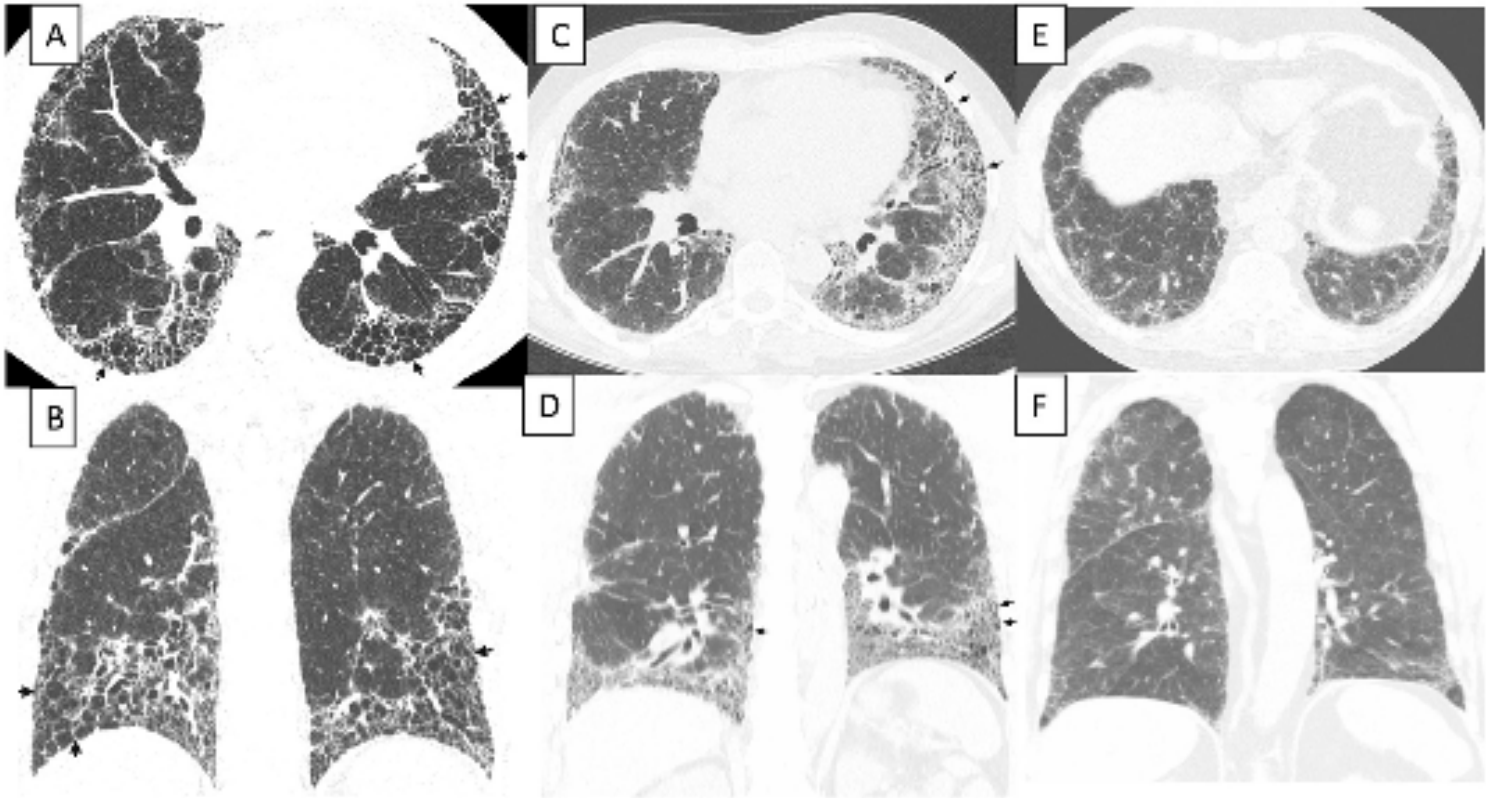
| Category | Clinical–Radiologic–Pathologic Diagnoses | Associated Radiologic and/or Pathologic–Morphologic Patterns |
|---|---|---|
| Chronic fibrosing IP | Idiopathic pulmonary fibrosis | Usual interstitial pneumonia |
| | Idiopathic nonspecific interstitial pneumonia | Nonspecific interstitial pneumonia |
| Smoking-related IP* | Respiratory bronchiolitis-interstitial lung disease | Respiratory bronchiolitis |
| | Desquamative interstitial pneumonia | Desquamative interstitial pneumonia |
| Acute/subacute IP | Cryptogenic organizing pneumonia | Organizing pneumonia |
| | Acute interstitial pneumonia | Diffuse alveolar damage |

*Definition of abbreviation*: IP = interstitial pneumonia.

*Desquamative interstitial pneumonia can occasionally occur in nonsmokers.

Travis W et al. *AJRCCM* 2013; 188:733-48




A
C
E
B
D
F

# Natural History

- Progressive decline in subjective and objective pulmonary function until eventual death
- Median survival time 2 to 3 years from time of diagnosis (maybe an underestimate)

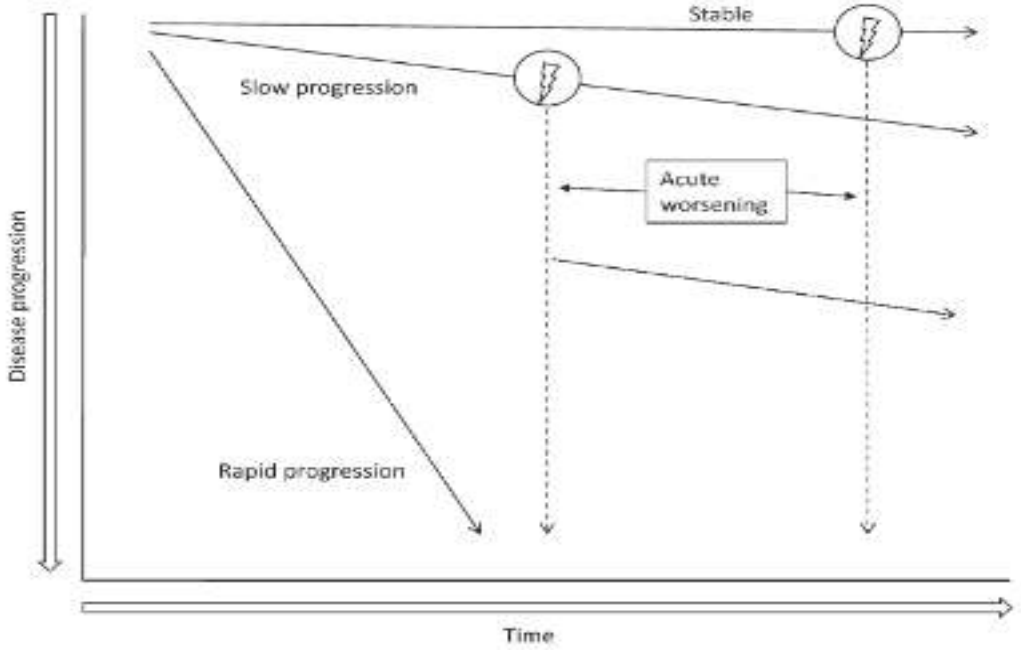



***Figure 4.*** Natural history of IPF. There appear to be several possible natural histories for patients with IPF. The majority of patients experience a slow but steady worsening of their disease ("Slow progression"). Some patients remain stable ("Stable"), while others have an accelerated decline ("Rapid progression"). A minority of patients may experience unpredictable acute worsening of their disease (lightning bolt), either from a secondary complication such as pneumonia, or for unrecognized reasons. This event may be fatal or may leave patients with substantially worsened disease. The relative frequency of each of these natural histories is unknown.

Raghu G et al. *AJRCCM* 2011; 183:788-824

## TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS

| |
|---|
| Baseline factors* |
| Level of dyspnea† |
| $D_{LCO}$ < 40% predicted |
| Desaturation ⩽ 88% during 6MWT |
| Extent of honeycombing on HRCT† |
| Pulmonary hypertension |
| Longitudinal factors |
| Increase in level of dyspnea† |
| Decrease in Forced Vital Capacity by ⩾ 10% absolute value |
| Decrease in $D_{LCO}$ by ⩾ 15% absolute value |
| Worsening of fibrosis on HRCT† |

*Definition of abbreviations*: 6MWT = 6-minute-walk test; $D_{LCO}$ = diffusion capacity for carbon monoxide; HRCT = high-resolution computed tomography.

* Baseline forced vital capacity is of unclear predictive value.

† Currently, there is no uniformity in approach to quantification.

Raghu G et al. *AJRCCM* 2011; 183:788-824

# Treatment

- Depends of type of ILD
- Steroids
- Smoking cessation
- Nintedanib
- Pirfenidone

THANK YOU