THE INTERSTITIAL LUNG DISEASES (ILDS)

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ILDs represent

- parenchyma of the lung
- alveolar epithelium
- capillary endothelium
- spaces between those structures
- perivascular and lymphatic tissues

Involve
**Histologically**

- **ILD**
- **Interstitial**
- **Basement membrane of the vascular structures**
- **Basement membranes of the epithelial cells**
ILD

- Inflammatory-fibrotic
- Infiltration of the alveolar walls (septa)
- Capillary endothelium
- Alveolar epithelial
INTRODUCTION

- Fibroblastic proliferation
- Excessive collagen deposition
- Histologic hallmarks of ILD
Dyspnea
Cyanosis
Nonproductive, hacking cough

Diffuse interstitial opacities on chest imaging studies; restrictive pulmonary function pattern

Bibasilar inspiratory ("Velcro") crackles

Weight loss

Cor pulmonale (late)

Elevated diaphragm
interstitial Lung Diseases

- progressive exertional dyspnea
- persistent nonproductive cough
- Hemoptysis
- Wheezing
- Chest pain
- interstitial opacities on CXR
Causes

- Idiopathic
- Organic
- Inorganic (Pneumoconiosis)
- CTD
- Drugs
- Sarcoidosis
PATHOGENESIS ILDs

- nonmalignant
- not infectious agents
- injury to fibrosis is not known?
- mechanisms of repair have common features
Inflammation and Fibrosis

- inflammation in the air spaces and alveolar walls
- Chronic
- adjacent portions of the interstitium and vasculature

Eventually causes

- interstitial fibrosis
ILD

- Irreversible scarring (fibrosis)
  - alveolar walls
  - Airways
  - vasculature
- often progressive
- ventilatory function and gas exchange
PATHOGENESIS OF PULMONARY FIBROSIS

Exogenous and endogenous stimuli

Dust, fumes, cigarette smoke, autoimmune conditions

Drugs, infections, radiation, other diseases

Microscopic lung injury: separated spatially and temporally

Intact Wound healing Aberrant

Genetic predisposition Autoimmune conditions

Lung homeostasis Pulmonary fibrosis
ILDs

- >200 known individual diseases
- diffuse parenchymal lung involvement
- Idiopathic
- Multiorgan process, CTDs
IDIOPATHIC INTERSTITIAL PNEUMONIAS

- IPF
- NSIP
- RB-ILD
- DIP
- COP
- AIP
- Rare IIPs include
  - LIP
  - idiopathic pleuroparechymal fibroelastosis
- Unclassifiable IIP
Histopathology

- predominant inflammation and fibrosis
- predominantly granulomatous reaction
Histopathology

- **Alveolitis, Interstitial Inflammation, and Fibrosis**
  - Known Cause
  - Unknown Cause

- **Granulomatous**
  - Known Cause
  - Unknown Cause
Histopathology

- **Alveolitis, Interstitial Inflammation, and Fibrosis**
  - Known Cause
    - Asbestos
  - Unknown Cause
    - IPF

- **Granulomatous**
  - Known Cause
    - HP
  - Unknown Cause
    - SARCOIDOSIS
CURRENT CLASSIFICATIONS

• HISTOPATHOLOGY AND CLINICAL SYNDROMES
  • IDIOPATHIC INTERSTITIAL PNEUMONITIDES
  • GRANULOMATOUS DISORDERS
  • CONNECTIVE TISSUE–RELATED ILDs
  • DRUG-INDUCED ILDs
  • PULMONARY VASCULITIC DISORDERS
  • UNKNOWN ORIGIN THAT EXHIBIT WELL-DEFINED SYNDROMES SUCH AS
    • PULMONARY LANGERHANS CELL HISTIOCYTOSIS (LCH)
    • LYMPHANGIOLEIOMYOMATOSIS
ILD

- Acute phase
- Chronic phase
- Rarely, recurrent
HISTORY
Duration of Illness

- Acute presentation (days to weeks), unusual
  - allergy (drugs, fungi, helminths)
  - acute interstitial pneumonia (AIP)
  - Hypersensitivity pneumonitis

*confused with atypical pneumonias*
DIAGNOSIS

• **SOME ILDs MANIFEST IN AN ACUTE FASHION**
  • ACUTE PNEUMONITIS DUE TO SYSTEMIC LUPUS ERYTHEMATOSUS
  • ACUTE HYPERSENSITIVITY PNEUMONITIS (HP)
  • SOME DRUG REACTIONS
  • ACUTE INTERSTITIAL PNEUMONIA

• **INFECTION OFTEN NEEDS TO BE RULED OUT IN THESE CASES**
HISTORY
Duration of Illness

- **Subacute presentation (weeks to months)**
- Sarcoidosis
- drug-induced ILDs
HISTORY
Duration of Illness

- chronic presentation (months to years)
  - IPF
  - Sarcoidosis
  - PLCH
  - Pneumoconioses
  - CTDs
DIAGNOSIS

- DELAYED
- HRCT
DIAGNOSIS

- Most ILDs
- IPF
- CHRONIC, PROGRESSIVE SYMPTOMS
Most patients with IPF are older than 60 years

- Sarcoidosis
- LAM
- PLCH

Ages of 20 and 40 years
Gender

- LAM / tuberous sclerosis exclusively premenopausal women
- CTDs women
- ILD in RA men
- Pneumoconioses men
Smoking History usually current or former smokers

- Two-thirds to 75% → **IPF** and **familial lung fibrosis**
- PLCH
- RB_ ILD
- DIP
DIAGNOSIS

• **ENVIRONMENTAL EXPOSURES**
  - EXPOSURE TO PET BIRDS OR HOT TUBS MAY SUGGEST HP

• **OCCUPATIONAL HISTORY**
  - PNEUMOCONIOSES ➡️ ASBESTOS AND SILICA EXPOSURE
  - BERYLLIOSIS
  - GRANULOMATOUS PNEUMONITIS IN INDOOR LIFEGUARDS EXPOSED TO MOLDS
Occupational History

- hypersensitivity pneumonitis
- Pigeon breeder’s disease & workplace (farmer’s lung)
- fever, chills, and an abnormal CXR
- symptoms may reappear
Past History

- Parasitic infections
- Travel history
DIAGNOSIS

• **The history**
  - Rash, dysphagia, arthritis, and Raynaud’s phenomenon

• Connective tissue disorder
DIAGNOSIS

- **POORLY CONTROLLED ASTHMA**
- RADIOGRAPHIC INFILTRATES
- CONSTITUTIONAL SYMPTOMS
- **CHURG-STRAUSS SYNDROME**
DIAGNOSIS

• **SEVERE SINUS DISEASE**

• **GRANULOMATOSIS WITH POLYANGIITIS GPA (WG)**
DIAGNOSIS

• Drug-induced ILD
Diagnosis

- Clinician
- Radiologist
- Pathologist
Approach

- Close communication between
- HRCT scanning
- Tissue examination

- Thoracoscopic lung biopsy
physical examination

- oxygen desaturation with exertion in early ILD.
- decreased chest expansion during inspection.
- Auscultation Velcro-like crackles at the lung bases.
- clubbing.
PHYSICAL EXAMINATION

- Skin rashes,
- Arthritis with joint deformities,
- Raynaud’s phenomenon,
- Dysphagia
- Connective tissue–related ILD such as
  - Dermatomyositis or polymyositis,
  - Progressive systemic sclerosis,
  - Mixed connective tissue disorder.
PHYSICAL EXAMINATION

- Evidence of right ventricular heart failure
- Jugular vein distention
- Cardiac gallop
- Loud P2 sound
- Leg edema

- Chronic hypoxemia and is often related to end-stage lung disease.
PHYSICAL EXAMINATION

- Tachypnea
- Bibasilar end-inspiratory dry crackles
- Scattered late inspiratory high-pitched rhonchi
- so-called inspiratory squeaks
- Bronchiolitis
- Cardiac examination is usually normal
- Pulmonary hypertension and cor pulmonale
- Cyanosis and clubbing of the digits
Clubbed fingers

Normal angle of nail base

Distal migration of nail bed
• EXAMINATION

Clubbing
Bibasal Crackles
Cor Pulmonale
Respiratory Effort ↑
Reduced Expansion
Cyanosis
Clinical Features

**Dyspnea (Progressive)**

**Cough (No Sputum)**

**Ex Tolerance**

**Weight Loss**

**Fatigue**

- **HISTORY**
  - Onset?
  - Time?
  - Progressive?

- **After HPCx:**
  - PMHx
  - Smoking
  - Pets
  - Exposure in Job/Hobby
  - Ask specific meds!
  - If confident ask CTD Sx
DIAGNOSIS

- **Laboratory Studies Eosinophilia**
- **Pulmonary Infiltrates and Peripheral Blood Eosinophilia**
CHEST RADIOGRAPH
UPPER- AND MID-LEVEL LUNG FIELDS

- SARCOIDOSIS,
- LCH
- LYMPHANGIOLEIOMYOMATOSIS
CHEST RADIOGRAPH
LOWER-LEVEL LUNG FIELDS

• IPF,
• ASBESTOSIS,
• MANY CONNECTIVE TISSUE–RELATED ILDS
CHEST IMAGING STUDIES
Chest X-Ray ILD

- **Bibasilar reticular pattern**
  - A nodular
    - mixed pattern of alveolar filling and increased reticular

- **Honeycombing**

- *CXR is nonspecific and usually does not allow a specific diagnosis*
Most forms ofILD produce a restrictive defect

- TLC
- FRC
- RV
PULMONARY FUNCTION TESTING

- **FEV1**
- **FVC**
- FEV1/FVC ratio is usually normal or increased
FORCED EXPIRATORY VITAL CAPACITY MANEUVER

Patient inspires maximally to total lung capacity, then exhales into spirometer as forcefully, as rapidly, and as completely as possible.
Curve shifted to right

TLC

RV

Volume (L)
Diffusing Capacity (DlCO)

- diffusing capacity of the lung for carbon monoxide
- common but nonspecific finding in most ILDs
- effacement of the alveolar capillary units
Pathways of O₂ and CO₂ diffuse

- Alveolus
- Surface-lining fluid
- Alveolar epithelium
- Basement membranes (fused)
- Capillary endothelium
- Plasma

Red blood cell
- Membrane
- Intracellular fluid
- Hemoglobin molecules

\[ P_{O₂} = 150 \text{ mm Hg} \]
\[ P_{CO₂} = 0 \text{ mm Hg} \]

Atmospheric air at airway opening
• Accumulation of FBROBLASTS
• **TIS** thickenened interstitium
• Poor oxygenation with exercise,
• Increased lung stiffness exhibited
• Decreased compliance,
• Small lung volumes,
• Increased work of breathing
Arterial Blood Gas

- Resting ABG may be normal
- Significant hypoxemia during exercise or sleep
- Hypoxemia & respiratory alkalosis
- Carbon dioxide (CO2) retention is rare
- Usually a manifestation of end-stage disease
Small lung volumes
Idiopathic pulmonary fibrosis
Asbestosis

Preserved lung volumes
Sarcoidosis
Hypersensitivity pneumonitis
MIXED PATERNRS

- **LYMPHANGIOLEIOMYOMATOSIS**
  - Small airways are narrowed by the proliferation of surrounding abnormal smooth muscle–like cells.
  - Increased airway resistance and airflow obstruction.

- **SARC OIDOSIS**
  - Endobronchial disease with direct narrowing of the airways can occur leading to similar effects.
DIAGNOSIS

- **CLINICAL AND IMAGING DATA ARE INSUFICIENTLY SPECIFIC**
- **LUNG BIOPSY**
  - SURGICAL LUNG BIOPSY, A THORACOSCOPIC APPROACH
  - TBLB USEFUL FOR
    - SARCOIDOSIS
    - COP
    - HP
MANAGEMENT OF ILD

- Depends on the underlying cause
- Exposure avoidance for HP, smoking-related ILD, and drug-induced ILD.
- Immunosuppressants
- Supplemental oxygen and pulmonary rehabilitation
- Lung transplantation
Idiopathic Pulmonary Fibrosis
Idiopathic Pulmonary Fibrosis

- chronic, progressive fibrosing interstitial pneumonia
- un-known cause
- occurring primarily in older adults
- Limited to the lungs
- progressive worsening of dyspnea and lung function
- associated with a poor prognosis
Idiopathic Pulmonary Fibrosis

- 25% to 30% of ILDs
- clinical, radiographic, physiologic, and pathologic
- diagnosis of exclusion

- prevalence 0.8 to 65/100,000
- Incidence 0.4 to 27/100,000

- increase markedly with age
Clinical Features

**IPF**

- Middle age *50 and 70* years of age
- Insidious onset of *exertional breathlessness*
- Nonproductive cough
- Constitutional symptoms are uncommon
  - Weight loss, fever, fatigue, myalgias, or arthralgia
- Symptoms for months to years before definitive evaluation
  - 12 to 18 months
physical examination

- Bibasilar late inspiratory fine crackles (Velcro crackles)
- Clubbing of the fingers is seen in 40% to 75% late
- Cardiac examination is usually normal except in the middle or late
- Findings of pulmonary hypertension
  - (e.g., augmented P2, right-sided lift, tricuspid regurgitation, and S3 gallop)
- Corpulmonale
- Cyanosis late manifestation
- Spontaneous pneumothorax or pneumomediastinum is rare
Blood and Serologic Studies

- ESR ↑
- Low-level ANA titer positivity (≥40 and <1:320)
- RF (>60 IU/mL)
- CBC diff counts are usually normal
Chest Radiography

- peripheral reticular opacities
- netlike appearance of linear or curvilinear densities
- predominance at the lung bases
- A coarse reticular pattern or multiple cystic or honeycombed areas correlate with advanced disease and poor prognosis
diffuse bilateral lower lung predominant reticular opacities in a patient with idiopathic pulmonary fibrosis (IPF)
network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage IPF
High-resolution CT image of advanced IPF shows extensive honeycomb changes.

**cystic spaces 2 to 4 mm in diameter**
HRCT scan

- Honeycomb cysts in a basilar subpleural distribution
- Variously sized cystic spaces in several layers
- Ground-glass opacities are common
- Architectural distortion lung fibrosis
<table>
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<th>Usual interstitial pneumonia</th>
<th>Distribution</th>
<th>Imaging Features</th>
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<td>Basal, peripheral predominant</td>
<td>Reticulation, traction bronchiectasis/bronchiolectasis</td>
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<tr>
<td></td>
<td>May be asymmetric and patchy</td>
<td>Honeycombing</td>
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![Images](A,B,C)
If honeycombing is absent on HRCT atypical features such as
- ground-glass infiltrates
- lymphadenopathy,
- nodules,
- air trapping

- lung biopsy may be needed
Pulmonary function tests

- restrictive pattern
- reduced DICO
- arterial hypoxemia
- exaggerated or elicited by exercise
Diagnosis

- Other potential causes of ILD, such as
  - connective tissue disease
  - hypersensitivity pneumonitis
  - Asbestosis

- history, examination, & selected laboratory testing

must be ruled out by
No effective therapy for IPF
- Thalidomide appears to improve cough
- GERD therapy
- Antifibrotic drug: pirfenidone
- Lung transplantation

- Prednisone
- Azathioprine
- N-acetylcysteine (NAC)
- warfarin

*Increase the risks of hospitalization and death*
GRANULOMATOUS DISORDERS
INTERSTITIAL LUNG DISEASES WITH
GRANULOMA FORMATION
Interstitial Lung Diseases with Granuloma Formation

- granulomatosis with polyangiitis,
- HP
- chronic beryllium disease

- **sarcoidosis is the most common**
Sarcoidosis
Definition and Epidemiology

- multisystem granulomatous disorder of unknown cause
- lungs and thoracic lymph nodes
- Prevalence of 1 to 40 cases per 100,000 people worldwide
- sarcoidosis may be asymptomatic
- typically occurs in individuals between 10 and 40 years old
Noncaseating granulomas
Pathology Sarcoidosis

- Epithelioid histiocytes
- CD4+ T lymphocytes
- Giant cells
- Lymphocytes
- Connective tissue fibroblasts
Subepithelial noncaseating granuloma
Sarcoidosis commonly involved

- Upper respiratory system
- Lymph nodes
- Skin
- Eyes
Sarcoidosis

Virtually any other organ may be affected

- Liver
- bone marrow
- Spleen
- musculoskeletal system
- Heart
- salivary glands
- nervous system
Sarcoidosis

- The granulomas may be clinically silent
- Cause of these lesions is unknown
  - Inhaled antigens?
    - Mycobacteria and Propionibacterium?
    - Environmental substances?
- This inflammation may be self-limited
Sarcoidosis

- **Abnormal immune function**
- Cutaneous anergy
- exhibited in lung by an $\text{CD}4+/\text{CD}8+$ T lymphocytes
- **pro-inflammatory cytokines**
  - Interferon $\gamma$
  - Interleukin 12
  - TNF $\alpha$
- immunomodulatory therapy, especially with INF $\alpha$
- immune reconstitution syndrome
Clinical Presentation

acute

- incidentally on routine CXR of asymptomatic individuals
- **Löfgren syndrome**
  - Erythema nodosum
  - Fever
  - Arthritis
  - Hilar adenopathy
- **Uveoparotid fever (i.e., Heerfordt’s syndrome)**
  - Uveitis
  - Parotitis
  - Facial nerve palsy
- better outcomes than for other clinical presentations of sarcoidosis
Clinical Presentation
vague and chronic

- low-grade fevers
- Fatigue
- night sweats
- joint pains
Clinical Presentation
Respiratory manifestations

- *one third to one half of patients*
- shortness of breath
- Wheezing
- dry cough
- chest pain
Clinical Presentation
Skin manifestations

- erythema nodosum
- Plaques
- Nodules
- lupus pernio
  - violaceous, disfiguring, nodular lesion of the nose and cheeks
Erythema nodosum
Clinical Presentation
Ocular symptoms

- Common
- Onset of uveitis may eventually lead to the diagnosis
- Granulomatous extraocular organ involvement?
Clinical Presentation
Neurosarcoidosis

- cranial nerve palsies
- headache in the setting of lymphocytic meningitis
Clinical Presentation involve the heart

- Cardiomyopathy
- Arrhythmias and sudden cardiac death
  - conducting system by granulomatous infiltration
- Pulmonary hypertension
  - pulmonary fibrosis
  - Directly from granulomatous vasculitis
HILAR ADENOPATHY IN A PATIENT WITH SARCOIDOSIS
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<th>STAGE</th>
<th>RADIOGRAPHIC FINDINGS</th>
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<tr>
<td>0</td>
<td>Normal radiograph</td>
</tr>
<tr>
<td>I</td>
<td>Adenopathy without parenchymal abnormality</td>
</tr>
<tr>
<td>II</td>
<td>Adenopathy and parenchymal disease</td>
</tr>
<tr>
<td>III</td>
<td>Parenchymal disease without lymphadenopathy</td>
</tr>
<tr>
<td>IV</td>
<td>End-stage fibrosis</td>
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Sarcoidosis with interstitial infiltrates
SARCOIDOSIS

- Pulmonary function tests show restriction or obstruction
- Liver involvement may cause mild elevation of AST & ALT
  - cirrhosis and liver failure rare
- Hypercalcemia and hypercalciuria
- Kidney stones
- Elevated levels of ACE are common but are not specific
Diagnosis of sarcoidosis

- typical clinical, radiographic, and histologic picture
- diagnosis of exclusion
- Löfgren syndrome or uveoparotid fever may not require biopsy
- most patients require tissue biopsy of an affected organ
  - noncaseating granulomas
- ruling out other causes of granulomatous inflammation
  - mycobacterial infection
  - Necrotizing granulomas
Skin lesions

Lacrimal gland involvement

Bone destruction of terminal phalanges

Biopsy of nodule. Reveals typical sarcoidal granuloma (dense infiltration with macrophages, epithelioid cells, and occasional multinucleated giant cells)

Paralysis caused by involvement of facial (VII) nerve

Bilateral parotid gland involvement
Diagnosis of sarcoidosis

- **Bronchoscopy with TBLB** are positive for 50% to 60%
- Hemorrhage and pneumothorax

- **Endobronchial biopsies**

- **TBNA** of mediastinal and hilar lymph nodes
  - Endobronchial ultrasound guidance
Diagnosis of sarcoidosis

- ophthalmologic evaluation
- 24-hour collection of urine
- ECG & Holter monitoring
- If cardiac sarcoidosis is suspected
  - MRI or PET scanning
Treatment

- **Corticosteroids**
  - do not cause symptoms or complications
  - spontaneous remission

- extrapulmonary organ involvement

- **progressive pulmonary symptoms**

- 20 to 40 mg per day may be initiated

- steroid-sparing agents
  - methotrexate
  - Infliximab, an anti-TNF agent
Treatment

- erythema nodosum in the setting of Löfgren syndrome
  - nonsteroidal anti-inflammatory

- Other skin involvement
  - hydroxychloroquine or topical corticosteroids

- lupus pernio
  - infliximab

- anti-TNF agents
  - extrapulmonary disease not responding to conventional therapy
Treatment

- Anterior uveitis
  - topical steroids

- Other eye involvement
  - systemic corticosteroids

- Cardiac sarcoidosis
  - systemic corticosteroids

- Conduction system disease and arrhythmias
  - placement of pacemakers or automatic ICD

- Neurosarcoidosis and hypercalcemia
  - systemic steroid
Prognosis

- Spontaneous remission is common
- Death and disability occur rarely
- Acute sarcoidosis syndromes tend to remit and not recur
- 1/3 patients with sarcoidosis have chronic, progressive
- Some patients develop pulmonary fibrosis or other EOD
Summary

- Presents in many ways
- Usually lungs
- Any organ