INTERSTITIAL LUNG DISEASES (ILD)

Interstitial lung diseases are a group of pulmonary disorders characterized clinically by:

1. Radiologically diffused infiltrates.
2. Histologically by distortion of the gas exchanging units.
3. Physiologically by restriction of lung volumes and impaired oxygenation.

WHAT DOES THE TERM “INTERSTITIAL’ MEAN?

- This term when applied to these diseases is actually a misnomer.
- It implies that the inflammatory process is limited specifically to the area between the alveolar epithelial and capillary endothelial basement membranes.
- This group of pulmonary disorders frequently involves:
  1. alveolar epithelium
  2. alveolar space
  3. pulmonary microvasculature
  4. respiratory bronchioles
  5. larger airways
  6. pleura

DIFFERENTIAL DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

- Pneumoconiosis
- Drug-induced pulmonary injury
- Hypersensitivity pneumonitis (HP)
- Sarcoidosis
- Idiopathic pulmonary fibrosis (IPF)
- Bronchiolitis obliterans-organizing pneumonia (BOOP)
- Histiocytosis X (HX)
- Collagen vascular disease (Rheumatoid arthritis, Systemic lupus erythematosis, Polymyositis/dermatomyositis, Mixed connective tissue disease, Progressive systemic sclerosis)
- Granulomatous vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, Lymphomatoid granulomatosis)

DIFFERENTIAL DIAGNOSIS OF INTERSTITIAL LUNG DISEASE (cont…)

- Chronic eosinophilic pneumonia (CEP)
- Goodpasture's syndrome
- Pulmonary alveolar proteinosis (PAP)
- Lymphangioleiomyomatosis (LAM)
- Idiopathic pulmonary hemosiderosis
- Chronic pulmonary oedema
- Chronic gastric aspiration

DIAGNOSIS OF INTERSTITIAL LUNG DISEASE

The diagnosis of a specific ILD is based on:

1. Patient's history
2. Radiograph
3. Brochoalveolar lavage
4. Transbronchial biopsy
5. Open lung biopsy
6. Biopsy of extrathoracic tissues

ILD AND COMMON MODES OF CLINICAL PRESENTATION

1. Progressive dyspnea with exertion or a persistent dry cough are the usual complaints.
2. Respiratory symptoms associated with another disease such as a connective tissue disease.
3. No respiratory symptoms but abnormal chest radiograph. [Normal chest radiograph does not R/O ILD.]
4. Abnormal PFT, especially restrictive ventilatory pattern.

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

1. AGE:

Some of the ILDs are more common in certain age groups:

Age 20-40 years	-	Sarcoidosis
	-	CTD
	-	LAM
	-	EG
> 50years	-	Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis)

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

2. **GENDER:**

- *Premenopausal female:*
  LAM (lymphangioleiomatosis)
- *Female predominant:*
  ILD associated with CTD.
- *Male predominant:*
  ILD associated with RA
  Pneumoconiosis

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

3. SMOKING:

Diseases associated with smoker:

- EG (histocytosis X)
- Desquamative interstitial pneumonitis
- Respiratory broncholitis

Diseases less likely to be seen in smoker:

- Hypersensditivity pneumonitis
- Sarcoidosis

Pulmonary Hemorrhage is far more frequent in current smokers, with Good Pasture's syndrome.

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

4. DURATION:

i. Insidious over months or years (e.g., IPF)

ii. Acute (less than 3 weeks) (e.g. drug reaction, acute hypersensitivity pneumonitis, chemical exposure)

iii. Subacute: 3-12 weeks (e.g. Boop)

Table I. Duration of Illness Prior to Diagnosis

Acute (days to weeks) < 3 WKS

Acute idiopathin interstitial pneumonia (AIP, Hamman-Rich syndrome)
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Bronchiolitis obliterans with organizing pneumonia

Subacute (weeks to months) 3-12 WKS

Sarcoidosis
Some drug-induced ILDs
Alveolar hemorrahge syndromes
Idiopathic bronchiolitis obliterans with organizing pneumonia
Connective tissue disease (systemic lupus erythematosus or polymyositis)

Chronio (months to years) >12 WKS

Idiopathic pulmonary fibrosis
Sarcoidosis
Pulmonary histocytosis X

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

5. INTENSITY OF SYMPTOMS:

i. Minimal symptoms in the presence of grossly abnormal chest radiograph (e.g., sarcoidosis, histocytosis X).

ii. Severe symptoms in the presence of mild radiograph abnormalities (e.g., IPF, HP).

iii. Sudden worsening of dyspnea (particularly if assocaites with pleural pain) may indicate a spontaneous pneumothorax.

INTERSTITIAL LUNG DISEASE (ILD)

HISTORY

6. FAMILY HISTORY:

- Occasionally helpful.
- Autosomal dominant pattern:
  - IPF
  - Sarcoidosis
  - Neurofibromatosis
- Autosomal recessibe pattern:

  Gauchen’s disease

Table 2. Drug-Induced Interstitial Lung Disease

Antibiotics
- Nitrofurantoin, acute and chronic
- Sulfsalazine

Anti-inflammatory agents
- Aspirin
- Gold
- Pencillamine

Chemotherapeutic agents
- Antibiotics
  - Bleomycin sulfate
  - Mitomycin C
- Alkylating agents
  - Busulfan
  - Cyclophosphamide
  - Chlorambucil
  - Melphalan
- Antimetabolites
  - Azathioprine
  - Cytosine arabinoside
  - Methotrexate

Miscellaneous
- O2
- Drugs inducing pulmonary infiltrates and eosinophilia
- Radiation
- L-tryptophan

Drug-induced systemic lupus erythematosus
- Procainamide hydrochloride
- Isoniazid
- Hydralazine hydrochloride
- The hydantoins
- Pencillamine

Illicit drugs
- Heroin
- Methadone hydrochloride
- Propoxyphene hydrochloride (Darvon)
- Talc

Redrawn from Rosenow, EC, III, Martin WJ, II. Drug-induced interstitial lung disease. In: Interstitial Lung Disease, Schwarz, MI, King, TE, Jr, (Eds), Mosby Year Book, St. Louis, 1993, p. 255-270.

INTERSTITIAL LUNG DISEASE (ILD)

8. OCCUPATIONAL HISTORY AND SPECIFIC EXPOSURES

- Each of the following requires specific exposure:
  1. Pneumoconiosis
  2. Drug induced ILD
  3. Hypersensitivity pneumonitis (HP)
- The list of potentially injurious exposures grows each year and is impossible to commit to memory.
- The occupational history should begin with the patient's first job and continues chronologically.
- The patient should be asked to describe the exact duties at each job.
- A list of possible agent to which the patient may have been exposed.

CHEMICAL AGENTS ASSOCIATED WITH DIFFUSE PULMONARY INFILTRATES

CHEMICAL AGENT	SOURCE OF EXPOSURE
Nitrogen dioxide (Silo-Filler's disease)	Agriculture
Nitrogen oxide	Electrical arc welding
Chlorine	Accidental spills
Sulfur dioxide	Manufacturing: sulfites, sulfates, fumigants, commercial refrigerants
Oxygen	Mecahnical ventilation

INORGANIC DUSTS ASSOCIATED WITH DIFFUSE PULMONARY INFILTRATES (PNEUMOCONIOSIS)

Inorganic Dust	Occupations Associated with Exposure
Coal	Mining: cutting, loading
Graphite	Mining: printing, foundry work, nuclear reactors. Manufacturing: lubricants, rubber, alloys, steel electroplating, electrodes.
Silica, SiO2 (silicosis)	Mining, tunneling, foundry work, sandblasting, boiler-scaling. Manufacturing: ceramics, paints, varnishes, grinders
Asbestos, amosite srysotile crosotile (asbestosis)	Primary processing: mining, mills. Secondary uses: pipefitting, boiler work, ship manufacturing and repair, insulation work, construction, sheetmetal work, masonry, carpentry, automotive industry. Manufacturing: textiles, paper, cement, insulation, friction materials. Exposure to contaminated air: near mines and plants. Spouses of asbestos workers.

INORGANIC DUSTS ASSOCIATED WITH DIFFUSE PULMONARY INFILTRATES (PNEUMOCONIOSIS) cont...

Inorganic Dust	Occupations Associated with Exposure
Talc	Mining, Manufacturing: leather, paper, rubber, textiles, ceramic tiles, roofing material, paints, drugs, insecticides, herbicides, talc powder.
Mica, AlSO4	Manufacturing: stove or furnace windows, insulation. Additive: animal feed, chemicals, herbicides, insecticides, fungicides, fertilizer.
Iron	Electric arc welding, boiler scaling. Mining: iron ore. Manufacturing: iron, stell, foundry, silver polish.
Silver or iron	Jewelry making
Tin (stannosis)	Mining: tine ore

SYMPTOMS OF INTERSTITIAL LUNG DISEASE

1. **Dyspnea**
2. **Cough:**
   - A dry cough is common and seen in conditions that involve the airways:
     - Sarcoidosis
     - Boop
     - Broncholitis obliterans
     - Respiratory broncolitis
     - Pulmonary histocytosis X
     - Hypersensitivity pneumonitis
     - Lymphangitic carcinomatosis
   - Productive cough is unusual.

SYMPTOMS OF INTERSTITIAL LUNG DISEASE (cont…)

3. **Wheezing** is an uncommon symptoms:
   - Lymphangitic carcinomatosis
   - Chronic eosinophilic penumonia
   - Chung-Strauss syndrome
   - Respiratory bronchiolitis

4. **Chest pain** is an uncommon symptoms:
   - Pleuritic chest pain may occur in ILD, associated with RA/SLE, drug-induced disorders
   - Substernal discomfort is common in sarcoidosis

SYMPTOMS OF INTERSTITIAL LUNG DISEASE (cont…)

5. **Hemoptysis:** invokes the differential diagnosis of diffuse alveolar haemorrhage syndromes, pulmonary veno-occlusive disease, mitral stenosis, LAM, granulomatous vasculitides.

   New onset of hemoptysis in a patient with known ILD suggests a complicating malignancy.

6. **Fever:** IPF, RA, PSS are almost never associated with fever.

SYMPTOMS OF INTERSTITIAL LUNG DISEASE (cont…)

7. **Extra thoracic manifestations:**

   i. Nasal discharge or other upper airway symptoms that suggest Wegener's granulomatosis.

   ii Arthritis: CVD, sarcoidosis or granulomatous vasculitides.

   iii. IPF: arthralgias but never true synovitis.

   iv. Skin rashes: common to sarcoidosis, CVD and granulomatous vasculitis.

SYMPTOMS OF INTERSTITIAL LUNG DISEASE (cont…)

v. Neurological manifestation:
   - CNS symptoms
   - after lymphomatoid granulomatosis
   - mononuritis multiplex
   - Churg-Strauss syndrome
   - proximal muscle weakness is one of the diagnostic criteria for PM/DM

vi. Dysphagia - PM/DM or PSS

INTERSTITIAL LUNG DISEASE (ILD)

PHYSICAL EXAMINATION

- Little diagnostic specificity.
- Diffuse crackles: presence or absence adds little. May be present in the presence of normal c-xray.
- “Velcro rales” are common in most forms of ILD. They are less likely to be heared in sarcoidosis.
- Inspiratory squeaks typical of Boop.
- Clubbing: most commonly seen in IPF but non-specific. Rare in EG, sarcoidosis, HP.
- Cor pulmonale.
- Cynosis in late stage of ILD.
- Extrathoracic findings: directive but not diagnostic.

LABORATORY EVALUATION

- Peripheral eosinophilia > 10%
  - Chung-Strauss syndrome
  - Chronic eosinophilic pneumonia
- Abnormal renal function:
  - Pulmonary-renal syndromes
- Precipitating antibodies to specific antigens: markers of exposure sensatization).
- ANCA/Anti-GBM
- RF/ANA/Anti-DNA

LABORATORY FINDINGS IN THE INTERSTITIAL LUNG DISEASE

Abnormality	Associated Condition
Leukopenia	Sarcoidosis, connective tissue disease, lymphoma, drug-induced
Eosinophilia	Eosinophilic pneumonia, sarcoidosis, systemic vasculitis, drug-induced (sufa, methotrexate)
Thrombocytopenia	Sarcoidosis, connective tissue disease, drug-induced, Gaucher's disease
Hemolytic anemia	Connective tissue disease, sarcoidosis, lymphoma, drug-induced
Normocytic anemia	Diffuse alveolar hemorrhage syndromes, connective tissue disease, lymphangitic carcinomatosis
Urinary sediment abnormalities	Connective tissue disease, systemic vasculitis, drug-induced
Hypogammaglobulinemia	Lymphocytic interstitial pneumonitis
Hypergammaglobulinemia	Connective tissue disease, sarcoidosis, systemic vasculitis, lymphocytic interstitial pneumonia, lymphoma
Serum immune complexes	Idiopathic pulmonary fibrosis, lymphocytic interstitial pneumonitis, systemic vasculitis, connective tissue disease, eosinophilic granuloma
Serum angiotensin-converting enzyme	Sarcoidosis, hypersensitivity pneumonitis, silicosis, Gauche's disease
Antibasement membrane antibody	Goodpasture's syndrome
Antineutrophil cytoplasmic antibody	Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangitis
Serum precipitating antibodies	Hypersensitivity pneumonitis
Lymphocyte transformation test	Chronic beryllium disease, aluminum potroom workers disease, gold-induced pneumonitis
Elevation of LDH	Alveolar proteinosis, idiopathic pulmonary fibrosis

Redrawn from Schwarz, MI, King TE, Jr, Cherniack, RM. General principles and diagnostic approach to the interstitial lung disease. In: Murray, JF, Nadel JA (Eds), Textbook of Respiratory Medicine, 2nd ed, Philadelphia, WB Sauders Co., 1994, pp. 1803-1826.

INTERSTITIAL LUNG DISEASE (ILD)

PULMONARY FUNCTION TEST

- Most of the ILD have a restrictive defect.
- Smoking history should be considered
- Mixed pattern:
  - Sarcoidosis
  - Hypersensitivity Pneumonitis (HP)
  - Histocytosis X
  - Lymphangioleiomyomatosis (LAM)
  - Wegener's granulomatosis
  - Broncholitis obliterans organizing pneumonia (BOOP) rarely present with mixed pattern

INTERSTITIAL LUNG DISEASE (ILD)

PULMONARY FUNCTION TEST

- Moderate - severe reduction in DLCO but normal lung volumes in a patient with ILD suggest:
  - COPD with ILD
  - Pulmonary Vascular Disease
  - Pulmonary histocytosis X
  - Lymphangioleiomyomatosis
- A reduction in DLCO is common but nonspecific.
- The severity of the DLCO reduction does not correlate well with disease stage.

INTERSTITIAL LUNG DISEASE (ILD)

CHEST RADIOGRAPH

- ILD is often suspected on the basis of an abnormal chest x-ray.
- Review all previous films to assess the rate of change in disease activity.
- Remember, chest radiograph is normal in 10% of patients with ILD (particularly those with HP).

INTERSTITIAL LUNG DISEASE (ILD)

CHEST RADIOGRAPH

- Interstitial pattern:
  - Reticular
  - Linear
  - Ground glass (should be limited to HRCT Technique)
  - Reticonodular
  - Nodular
- These patterns are of limited value.
- They are poorly predictive of histology.
- The distribution of disease, pleural involvement, hilar/mediastinal adenopathy and pneumothorax, help to narrow the differential diagnosis.

Helpful Radiographic Patterns in the Differential Diagnosis of Interstitial Lung Disease

Peripheral lung zone predominance

- Bronchiolitis obliterans with organzing pneumonia
- Eosinophilic pneumonia

Upper zone predominance

- Granulomatous disease
  - Sarcoidosis
  - Pulmonary histiocytosis X (eosinophilic granuloma)
  - Chronic hypersensitivity pneumonitis
  - Chronic infectious diseases (e.g., tuberculosis, histoplasmosis)
- Pneumoconiosis
  - Silicosis
  - Berylliosis
  - Coal miners' pneumoconiosis
  - Hard metal disease
- Miscellaneous
  - Rheumatoid arthritis (necrotic nodular form)
  - Ankylosing spondylitis
  - Radiation fibrosis
  - Drug-induced (amiodarone, gold)

Lower zone predominance

- Idiopathic pulmonary fibrosis
- Rheumatoid arthritis (associated with usual interstitial pneumonia)
- Asbestosis

Helpful Radiographic Patterns in the Differential Diagnosis of Interstitial Lung Disease (cont…)

Multiple Nodules (>5mm)
- Sarcoidosis
- Vasculitis
- Wegener's granulomatosis
- Lymphomatoid granulomatosis
- Systemic lupus erythematosus
- Histiocytosis X
- Rheumatoid nodules
- Sjorgren's syndrome

Hilar/Mediastinal Adenopathy
- Sarcoidosis
- Berylliosis
- Histiocytosis X

Pleural Plaques, Bilateral
- Asbestosis

Pleural Effusion
- Rheumatoid lung disease
- Systemic lupus erythematosus
- Sarcoidosis (rare)

Spontaneous Pneumothorax
- Lymphangioleimyomatosis
- Histiocytosis X
- Idiopathic pulmonary fibrosis

Lobar/Segmental Infiltrates
- Chronic eosinophilic pneumonia (usually in lung periphery)
- Bronchiolitis obliterans - organizing pneumonia

Helpful HRCT Patterns in the Differential Diagnosis of Interstitial Lung Disease

Normal
Hypersensitivity pneumonitis
Sarcoidosis
Brochiolitis obliterans
Asbestosis
Distribution of disease within the lung
- **Peripheral lung zone**
  - Idiopathic pulmonary fibrosis
  - Asbestosis
  - Connective tissue disease
  - Bronchiolitis obliterans with organizing pneumonia
  - Eosinophilic pneumonia
- **Central disease (bronchovascular thickening)**
  - Sarcoidosis
  - Lymphangitic carcinoma
- **Upper zone predominance**
  - Granulomatous disease
    - Sarcoidosis
    - Pulmonary histiocytosis X (eosinophilic granuloma)
    - Chronic hypersensitivity pneumonitis
    - Chronic infectious diseases (e.g., tuberculosis, histoplasmosis)
  - Pneumoconiosis
    - Silicosis
    - Berylliosis
    - Coal miners' pneumoconiosis
- **Lower zone predominance**
  - Idiopathic pulmonary fibrosis
  - Rheumatoid arthritis (associated with usual interstitial pneumonia)
  - Asbestosis

Helpful HRCT Patterns in the Differential Diagnosis of Interstitial Lung Disease

Type of opacities within the lung

Airspace opacities

Haze or ground glass attenuation

- Hypersensitivity pneumonitis
- Desquamative interstitial pneumonia
- Respiratory bronchiolitis-associated interstitial lung disease
- Drug toxicity
- Pulmonary hemorrhage

Lung consolidation

- Chronic or acute eosinophilic pneumonia
- Bronchiolitis obliterans with organizing pneumonia
- Aspiration (lipid pneumonia)
- Alveolar carcinoma
- Lymphoma
- Alveolar proteinosis

Reticular opacities

- Idiopathic pulmonary fibrosis
- Asbestosis
- Connective tissue disease
- Hypersensitivity pneumonitis

Nodules

- Hypersensitivity pneumonitis
- Respiratory bronchiolitis-associated interstitial lung disease
- Sarcoidosis
- Pulmonary histiocytosis X
- Silicosis
- Coal miners' pneumoconiosis
- Metastatic cancer

Isolated lung cysts

- Pulmonary histiocytosis X
- Lymphangioleiomyomatosis
- Chronic PCP

ROLE OF LUNG BIOPSY

- Not required to make the diagnosis in all patient with ILD.
- However, it is not frequently possible to reach a definitive diagnosis or to stage a disease without examination of lung tissue.
- Indication for lung biopsy:
  - to assess disease activity
  - to exclude neoplasm or infection
  - to identify a more treatable condition
  - to establish a definitive Dx before starting a treatment with serious side effects
  - to provide a specific diagnosis in patients with:
    >> atypically or progressive pattern
    >> a normal or atypical chest x-ray features

BRONCHOSCOPY

- It is often the initial procedure of choice.
- Endobronchial lesions:
  - Sarcoidosis
  - Wegener's granulomatosis - Inflammation and stricture of the major airways
- Transbronchial bx:
  - Diagnostic: Sarcoidosis (75-80%)
    Lymphangitic carcinomatosis (80%)
    Eosinophilic pneumonia
    Pulmonary alveolar proteinosis
    Pulmonary histocytosis X
    Good pasture's syndrome

BRONCHOSCOPY
(cont…)

- BAL: normal count:
  - CD4:CD8 = 1.5
  - Macrophage 85%
  - Lymphocyte 5-10%
  - Neutrophils ≤ 2%
  - Eosinophils ≤ 1%

- Cytologic analysis:
  - PAS stain ´PAP
  - Monoclonal abx (OKT6) ´Histocytosis X
  - Asbestos exposure: one asbestos body per mL

BRONCHOSCOPY
(cont…)

- The utility of BAL in the clinical assessment of disease progression or response to therapy still to be established.
- CD4:CD8: > 2 is seen in sarcoidosis, TB, fungal infection.
- CD4: CD8 < 1 is seen in hypersensitivity pneumonitis.

SURGICAL BIOPSY

Video-assisted thoracoscopic lung biopsy is the preferred method of obtaining lung tissue.

Relative contraindications:

- Serious cardiovascular disease
- Radiographic evidence of diffuse end-stage disease (honey combing)
- Severe pulmonary dysfunction

CHEST RADIOGRAPHIC PATTERNS

Multiple Nodules

- Sarcoidosis
- Vasculitis
  - Wegener's granulomatosis
  - Lymphomatoid granulomatosis
- Systemic lupus erythematosis
- Histiocytosis X
- Rheumatoid nodules
- Sjorgren's syndrome

Hilar/Mediastinal Adenopathy

- Sarcoidosis, Berylliosis,
- Histiocytosis X

Pleural Plaques, Bilateral

- Asbestosis

Pleural Effusion

- Rheumatoid lung disease
- Systemic lupus erythematosis
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Lobar/Segmental Infiltrates

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- Bronchiolitis obliterans - organizing pneumonia