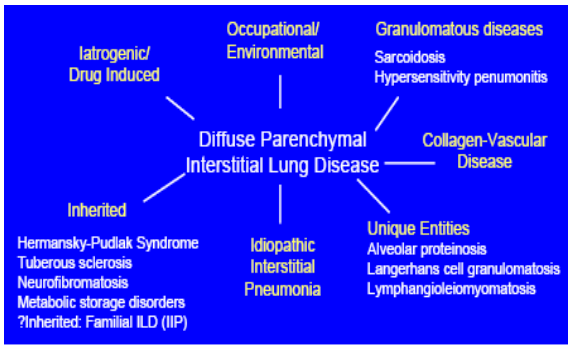
ILD-INTRODUCTION

- Interstitial lung disorders are heterogeneous group of lung disorders with variable degree of pulmonary fibrosis
- Diffuse parenchymal lung disease is, perhaps a more appropriate descriptive term.
- Incidence ranges from 3-26/1,00,000 per year.
- Prevalence of preclinical and undiagnosed ILD is estimated to be 10 times that of clinical recognized disease.
- IPF is the most common form representing at least 30 percent of the incident cases.

ILD-INTRODUCTION

- Syndromic diagnosis with common clinical features
  - Exertional dyspnea
  - Bilateral diffuse infiltrates on chest radiograph
  - Restrictive lung defects, ↓DLCO, abnormal (PAo2-Pao2)
  - Absence of pulmonary infection and neoplasia
  - Histopathology: varied degrees of fibrosis and inflammation, with or without evidence of granulomatous or secondary vascular changes in pulmonary parenchyma



ILD-ONSET OF SYMPTOMS

- Acute presentation (days to weeks)
  - Acute idiopathic interstitial pneumonia
  - Eosinophillic pneumonia
  - Hypersensitive pneumonitis
  - BOOP
- Sub-acute presentation (weeks to months)
  - Sarcoidosis
  - Drug induced ILD
  - Alveolar hemorrhage syndromes
  - COP
  - CV-ILD
- Chronic presentation (months to years)
  - IPF
  - Sarcoidosis
  - PLCH
- Episodic DPLD'S
  - Eosinophillic pneumonia
  - Hypersensitivity pneumonitis
  - Vasculitides/pulmonary hemorrhages
  - Churg-Strauss syndrome
  - COP

ILD-SYMPTOMS

- Respiratory symptoms
  - Exertional dyspnea
  - Cough
    - nonspecific, but may be an initial complaint
    - Cough as initial complaint raises possibility of superimposed/coexistent airway disease
      1. RB-ILD
      2. Sarcoidosis
      3. Hypersensitivity pneumonitis
      4. Pulmonary Langerhans cell histiocytosis
      5. Lipoid pneumonia
    - Productive cough – long standing IPF with traction bronchiectasis

ILD-SYMPTOMS

- Respiratory symptoms (contd)
  - Hemoptysis
    - Diffuse alveolar hemorrhages (33% - no hemoptysis)
    - Lymphangioleiomyomatosis
    - Tuberous sclerosis
    - Pulmonary veno-occlusive disease
    - Drugs such as D-pencillamine
    - Known case of ILD R/o
      1. Malignancy
      2. Pulmonary embolism
      3. Infection.

ILD-SYMPTOMS

- Respiratory symptoms (contd)
  - Chest pain
    - Pleuritis – SLE (50%), RA(25%)& other collagen vascular diseases
    - Pneumothorax (40%)
    - Substernal chest pain - sarcoidosis
  - Wheezing
    - Airway diseases
      1. Churg-Strauss
      2. Chronic eosinophillic pneumonia
    - Endobronchial lesions
      1. Sarcoidosis
      2. Wegner's
      3. Amyloidosis
      4. Inflammatory bowel disease

ILD-SYMPTOMS

- Non Respiratory symptoms
  - Arthritis – Sarcoidosis and collagen vascular diseases
  - Ocular – Sarcoidosis, collagen vascular diseases & HLA-B27 associated diseases
  - Skin and muscle - Polymyosistis
  - Sicca syndrome – Sarcoidosis, Sjogrens and other CVD
  - GERD – IPF and Scleroderma
  - Lower GI symptoms – Inflammatory bowel disease
  - Recurrent sinusitis – Wegners granulomatosis
  - Neurological symptoms – Sarcoidosis, Vasculitis
  - Epilepsy & mental retardation – Tuberous sclerosis
  - Diabetes inspidus – Sarcoidosis, PLCH

ILD-DEMOGRAPHY

- AGE
  - Age - 20-40 Years
    1. Sarcoidosis
    2. Connective tissue disease-associated ILD
    3. Lymphangioleiomyomatosis
    4. Pulmonary Langerhans cell histiocytosis,
    5. Inherited forms of ILD
  - Age >50 Years
    1. IPF – appx 2/3 of pts are >60 years old at time of diagnosis

ILD-DEMOGRAPHY

- SEX
  - Male predominance
    - PLCH
    - Pneumoconiosis
    - Rheumatoid arthritis – ILD
  - Female predominance
    - LAM
    - Tuberous sclerosis
    - Hermansky-Pudlak syndrome
    - Collagen vascular disorders

ILD-HISTORY

- Smoking
  - Current or former smokers
    1. RB-ILD (100%)
    2. LCH (90%)
    3. DIP (90%)
    4. IPF
  - Never or former smoker
    1. Sarcoidosis
    2. Hypersensitive pneumonitis
  - Active smoking – increased complications in good pasture syndrome

ILD-HISTORY

Medication history

- Temporal onset of events
  - Antibiotics - Sulfasalazine, Nitrofurantoin, Ethambutol & Minocycline
  - Anti-inflammatory – Aspirin, NSAIDS, Gold & Pencillamine
  - Anti-arrhythmics – Amiodorane, B-blockers
  - Anti-convulsants – Carbamazepine, Dilantin
  - Diuretics – Hydrochlorothiazide
  - Chemotheraupatic agents
    - Alkylating agents – Cyclophosphamide, Melphalan, Busulfan, Chlorambucil, Procarbazone
    - Anti-metabolites – Methotrexate, Azathioprine
    - Nitrosourea's – Carmustine, Lomustine, Semustine
    - Antibiotic's – Mitomycin, Bleomycin
    - Others – Etopside, Taxol's, Thalidomide, INF-α, Gefltinib

ILD-HISTORY

Medication history (Contd)

- Temporal onset of events (Contd)
  - Drug induced SLE – INH, Procainamide, Hydralazine
  - Illicit drugs – Heroin, Methadone, Propoxyphene, Cocaine & Talc
  - Miscellaneous- Radiation, Oxygen, L-Tryptophan, Bromocriptine
  - Alternative medicines (herbal, naturopathies, vitamin & mineral supplements)
  - OTC, Oily nose drops, Petroleum products, Amino acid supplements
- Symptoms weeks to years after the drug has been discontinued (eg, carmustine).

ILD-HISTORY

Occupational history

- Detailed history of occupation
  - Pneumoconioses – miners
  - Silicosis – sand blasters & granite workers
  - Asbestosis – welders, electricians, mechanics, workers with brakes, shipyard workers
  - Berylliosis – aerospace, nuclear, computer & electronic industries
  - Dental worker pneumoconiosis – dental workers
  - Hypersensitive pneumonitis – farm workers, poultry workers, bird breeders
- The degree of exposure, duration, latency of exposure, and the use of protective devices should be elicited

ILD-HISTORY

- Environmental exposure history
  - Exposures to pets (especially birds)
  - Air conditioners
  - Humidifiers
  - Hot tubs
  - Evaporative cooling systems
  - Passive exposure in the family

ILD-HISTORY

- Family history
  - Autosomal dominant pattern (with or without incomplete penetrance)
    - Idiopathic pulmonary fibrosis
    - Sarcoidosis
    - Tuberous sclerosis
    - Neurofibromatosis
  - Autosomal recessive pattern
    - Niemann-Pick disease
    - Gaucher's disease
    - Hermansky-Pudlak syndrome

ILD-SIGNS

Pulmonary

- Crackles
  - Dry, velcro , end inspiratory, predominantly bibasilar
  - Common in many chronic ILD
  - 80% of cases of IPF
  - Less common in granulomatous diseases such as sarcoidosis, HP(25%)
- Inspiratory squeaks
  - Mid inspiratory, high pitched
  - Seen in Primary bronchiolitis
  - Airway centred pathologies – hypersensitive pneumonitis

ILD-SIGNS

Pulmonary (contd)

- Clubbing
  - Common – IPF (50%), DIP(50%), Asbestosis(43%), chronic HP
  - Rare – RB-ILD
  - Uncommon – Sarcoidosis, Acute ILD, COP, LIP, CVD-ILD
- Cor pulmonale
  - CVD- ILD (scleroderma)
  - Veno occlusive diseases
  - Advanced fibrosis (IPF, vital capacity <50%, DLCO <30%)

ILD-SIGNS

Extra Pulmonary

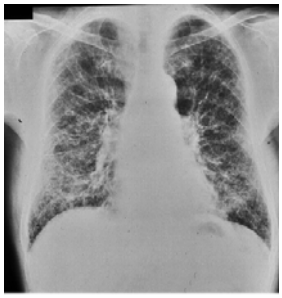
- Skin abnormalities, lymphadenopathy, hepatosplenomegaly – sarcoidosis.
- Maculopapular skin rashes – amyloidosis, CVD, neurofibromatosis, tuberous sclerosis, LCH, churg strauss, drug induced.
- Erythema nodosum - Sarcoid, Behcets, IBD.
- Subcutaneous nodules – rheumatoid arthritis, neurofibromatosis.
- Proximal muscle weakness - polymyositis.
- Arthritis – CVD, IBD, Sarcoid, Behcets, Ankylosing spondylitis.
- Sicca syndrome – sjogrens, sarcoidosis, CVD
- Uveitis - IBD, Sarcoid, Behcets, Ankylosing spondylitis.
- Scleritis – vasculitis, SLE, RA, Scleroderma, sarcoidosis.
- Systemic HTN – CVD, Neurofibromatosis, DAH syndromes
- Neurological – sarcoid, behcets, LCH
- Arthralgias are also seen in IPF

ILD-INVESTIGATIONS

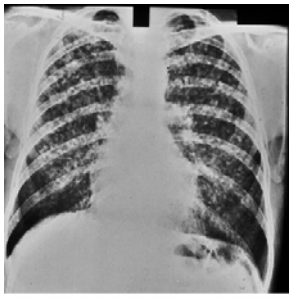
CHEST XRAY

- Normal CXR doesn't rule out ILD (10% normal- HP)
- All previous radiology to be reviewed
- Most common radiological abnormalities are
  - Reticular
  - Nodular
  - Mixed (alveolar filling + interstitial markings)
- Distribution and appearance of abnormalities help in narrowing the diagnosis
- The correlation between the roentgenographic pattern and the stage of disease (clinical or histopathologic) is generally poor.
- Only honeycombing (small cystic spaces) correlates with pathologic findings and, when present, portends a poor prognosis.

ILD-INVESTIGATIONS-CXR



Reticular opacities Standard International Labor Office film for small irregular s opacities, less than 1.5 mm in diameter (reticular opacities). Courtesy of Paul Stark, MD.



Small, rounded nodules Standard ILO film for small rounded opacities, 3–10mm in diameter. Courtesy of Paul Stark, MD.

ILD-RADIOGRAPHY

- Normal CXR
  - Hypersensitive pneumonitis
  - Sarcoidosis
  - Connective tissue diseases
  - Bronchiolitis obliterans
  - IPF (early stage)
  - Asbestosis
  - Lymphangioleiomyomatosis
- Alveolar opacities
  - Pulmonary hemorrhage
  - Eosinophillic pneumonia
  - Bronchiolitis with organizing pneumonia
  - Lupus pneumonitis
  - Alveolar proteinosis

ILD-RADIOGRAPHY

- Reticular or linear opacities
  - Peripheral lung zone predominance
    1. Eosinophillic pneumonia
    2. Bronchiolitis with organizing pneumonia
  - Upper zone predominance
    1. Granulomatous – sarcoidosis, LCH, Chronic hypersensitivity pneumonitis
    2. Pneumoconiosis – silicosis, berylliosis, coal workers pneumoconiosis, hard metal disease
    3. Miscellaneous – rheumatoid arthritis (necrobiosis nodular), cystic fibrosis, ankylosing spondylitis, radiation pneumonitis, drugs (gold, pencillamine
  - Lower zone predominance
    1. IPF
    2. Rheumatoid arthritis (UIP)
    3. Asbestosis
    4. Acute hypersensitivity pneumonitis

ILD-RADIOGRAPHY

- Endstage or honey combing
  - Upper zone predominance – sarcoidosis, lymphangioleiomyomatosis, LCH, chronic hypersensitivity pneumonitis.
  - Lower zone predominance – IPF, Rheumatoid arthritis (UIP), Asbestosis.
- Increased lung volumes
  - Lymphangioleiomyomatosis
  - LCH
  - Tuberous sclerosis
  - Neurofibromatosis
  - Sarcoidosis (stage 3)
  - Chronic hypersensitivity pneumonitis
  - IPF and smoker
  - Respiratory bronchiolitis
  - Bronchiolitis obliterans

ILD-RADIOGRAPHY

- Pneumothorax
  - Lymphangioleiomyomatosis
  - LCH
  - Tuberous sclerosis
  - Neurofibromatosis
- Kerley B lines
  - LAM
  - Lymphangitis carcinomatosis
  - Amyloidosis

ILD-RADIOGRAPHY

- Pleural involvement
  - Asbestosis
  - Connective tissue disorders
  - Lymphangioleiomyomatosis
  - Sarcoidosis
  - Amyloidosis
  - Radiation pneumonitis
  - Drug induced (Nitrofurantoin)
- Hilar or mediastinal lymphadenopathy
  - Sarcoidosis
  - Berylliosis
  - Silicosis
  - Collagen vascular disorders
  - Amyloidosis
  - Lymphoma
  - Kaposi's sarcoma

ILD-RADIOGRAPHY

- Subsegmental migratory infiltrates
  - Churg-Strauss syndrome
  - Allergic bronchopulmonary aspergillosis
  - Tropical/pulmonary interstitial eosinophilia
  - Bronchiolitis obliterans with organizing pneumonia
- Recurrent infiltrates in same location
  - Chronic eosinophillic pneumonia (upper lobes/peripheral)
  - Idiopathic BOOP
  - Drug induced
  - Realpse/recall radiation pneumonitis

ILD-RADIOGRAPHY

- Computed topography (HRCT)
  - HRCT more sensitive (94% compared to CXR – 80%))
  - Also identifies mixed patterns , additional pleural, hilar or mediastinal abnormalities
  - Shows better correlation with physiological impairment
  - Useful guide for selection of sites for BAL or biopsy
  - Normal HRCT would not exclude the presence of microscopic ILD in patients with high test probability.
  - Strength of HRCT lies in ability to give an overall assessment on severity of the irreversible changes (honeycombing and fibrosis).
  - Extent of fibrosis on HRCT shows 80%sensitivity and 85% specificity in predicting survival.

ILD-HRCT

- Useful HRCT patterns in ILD
  - Reticular, honeycombing, traction bronchiectasis – IPF,CVD-ILD, asbestosis, sarcoidosis. Eosinophillic pneumonia
  - Air space opacity, ground glass – COP, CEP, AIP, AEP, PAP, Sarcoidosis
  - Nodules – Granulomatous diseases, pneumoconiosis, Rheumatoid arthritis
  - Cystic changes – LAM, PLCH, LIP, Tuberous sclerosis
  - Mosaic pattern – Air-trapping (constrictive bronchiolitis)

ILD-HRCT

- Ground glass changes are nonspecific.
- Presence of traction bronchiectasis and bronchiolectasis on HRCT does correlate with fibrosis.
- Honey combing also represents an irreversible fibrotic manifestation.
- Acute HP- multifocal ground glass attenuation despite normal CXR & significant clinical symptoms
- Smokers with RB-ILD have patchy ground glass attenuation & b/l interstitial infiltrates with normal lung volumes.
- IPF – patchy sub pleural and basilar fibrosis

ILD-PULMONARY FUNCTION TESTING

- Evaluation includes
  - Spirometry
  - Lung volumes
  - Diffusing capacity (DLCO)
  - Exercise induced evaluation
- Advantages
  - Objective assessment of functional status
  - Paring of the diagnosis
  - Grading the severity
  - Monitoring the response
- Limitations
  - Cannot diagnose specific ILD
  - Cannot distinguish between active lung inflammation and fibrosis

ILD-PULMONARY FUNCTION TESTING

- PFT Findings
  - ↓ Lung volumes (TLC, FRC,RV <80%)
  - ↓ FEV1, FVC With Normal or ↑FEV1/FVC
  - Reduced diffusing capacity (DLCO)
- Mechanism involved
  - Increased elastic recoil (restrictive lung disease)
  - Alveolar-capillary dysfunction
    - Effacement of alveolar capillary units
    - V/Q mismatch
- Measurement of diffusion capacity (DLCO)
  - DLCO reduction does not correlate well with disease stage
  - Normal lung volumes with moderate to severe reduction of DLCO
    - Emphysema and ILD
    - Pulmonary vascular disease
    - PLCH
    - LAM

ILD-PULMONARY FUNCTION TESTING

- Exercise affords most sensitive diagnostic and physiologic test for ILD
- Good correlation between degree of fibrosis and
  - Degree of arterial hypoxemia induced by exercise
  - PAo2-Pao2 difference
- Exercise induced physiological abnormalities
  - ↓Work rate & maximum oxygen consumption
  - High minute ventilation at sub maximal work
  - ↓ Peak minute ventilation
  - Failure of tidal volume to ↑ at sub maximal work, with disproportionate ↑ in respiratory rates
  - Increased heart rate
  - Progressive arterial hypoxemia
  - Widening of PAo2-Pao2 difference
  - Persistent metabolic alkalosis

ILD-PULMONARY FUNCTION TESTING

- Patterns of diagnostic utility
  - ↓MVV, MIP out of proportion to ↓ in FEV1
    - Polymyosistis
    - SLE
    - Scleroderma
  - Interstitial pattern on CXR with obstructive pattern
    - ILD superimposed with COPD
    - LAM (65-78%)
    - Sarcoidosis (>50%)
    - PLCH (4-33%)
    - Tuberous sclerosis
    - Hypersensitivity pneumonitis
  - ILD with asthma or recurrent bronchospasm
    - Churg-strauss
    - Sarcoidosis (endobronchial)
    - Tropical eosinophillia

ILD-OTHER INVESTIGATIONS

- Tuberculin test – negative in 2/3 of sarcoidosis patients
- Serum markers – Surfactant protein A&B, MCP-1 and KL-6
  - KL-6 – Highest sensitivity (94%), specificty (96%), and diagnostic accuracy (94%) for ILD.
  - The clinical role of markers in ILD unclear
- Gallium scan
  - Role in suspected extra thoracic Sarcoidosis, which is not accessible for biopsy
- ^{99m}Tc-DTPA aerosal clearence
  - ^{99m}Tc-DTPA aerosal clearence is an index of lung epithelial permability
  - Increased DTPA clearence is sensitive marker of inflammation.
  - May be useful in IPF, Sarcoidosis, pneumoconiosis, Hypersensitivity pneumonitis, radiation pneumonitis

ILD-BRONCHOALVEOLAR LAVAGE

- BAL is a minor extension of routine fiberoptic bronchoscopy and may help define the stage of disease and allow for the assessment of disease progression or response to therapy.
- However, the utility of BAL in the clinical assessment and management of ILD patients remains to be established.
- Diagnostic
  - Infectious agents
  - malignancy
- Diagnosis aided by special stains or studies
  - Langerhans cell granulomatosis
  - LAM
  - Pneumoconiosis
  - Alveolar proteinosis
  - Berylliosis (in vitro lymphocytic proliferative response)

ILD-BRONCHOALVEOLAR LAVAGE

- Bronchoalveolar lavage cellular profile
  - Lymphocytosis (>20% of cellularity)
    - Hypersensitive pneumonitis (60-80%)
    - Sarcoidosis (acute – 40-60%)
    - IPF (15-30%)
    - Berylliosis
    - Amiodorane
    - PLCH
    - Lymphoma/pseudolymphoma
  - Neutrophilia (>5% of cellularity)
    - IPF (15-40%)
    - COP (40-70%)
    - Inorganic dust disease
    - PLCH
    - Hypersensitivity pneumonitis (early)
    - Sarcoidosis (advanced)
    - Smoking (10%)

ILD-BRONCHOALVEOLAR LAVAGE

- Bronchoalveolar lavage cellular profile (Contd)
  - Eosinophilia (>5% of cellularity)
    - High count (>30%)
      1. Tropical pulmonary eosinophillia (40-70%)
      2. Eosinophillic pneumonia (>40%)
    - Mild to moderate count (5-30%)
      1. IPF (<10%)
      2. Sarcoidosis
      3. PLCH
      4. Drug induced
      5. CVD-ILD
  - Mast cells (>1%)
    1. Hypersensitivity pneumonitis
    2. COP (±)
    3. Advanced sarcoidosis

ILD-BIOPSY

- Indications for performing a lung biopsy

1. To provide a specific diagnosis,
   - Especially in a patient with atypical or progressive symptoms and signs
   - Normal chest x-ray or atypical radiographic features
   - Unexplained extra pulmonary manifestations
   - Unexplained pulmonary hypertension or cardiomegaly
   - Rapid clinical deterioration or sudden change in radiographic appearance.
2. To assess disease activity.
3. To exclude neoplastic and infectious processes that occasionally mimic chronic, progressive interstitial disease.
4. To identify a more treatable process than originally suspected.
5. To establish a definitive diagnosis and predict prognosis before proceeding with therapies which may have serious side effects.

ILD- TRANS BRONCHIAL BIOPSY

- Trans bronchial biopsy
  - Initial procedure of choice, especially when in peri bronchovascular areas
    1. Sarcoidosis
       - Diagnostic yield – 75-89% if a/w diffuse infiltrates
       - 44-66% if no parenchymal lesion on CXR
       - Endobronchial biopsy – 45-77%
    2. Lymphangitic carcinomatosis
    3. Eosinophilic pneumonia
    4. Goodpasture's syndrome
    5. Pulmonary Langerhans cell histiocytosis
  - Is diagnostic if an infectious agent or maligancy is detected.
  - Presence of giant cell granulomas are diagnostic of heavy metal pneumoconiosis

ILD- OPEN LUNG BIOPSY

- Indications -<65 yrs of age when diagnosis is unclear
  - H/o fever, wt loss, sweats and hemoptysis
  - Family h/o familial ILD or IPF
  - H/o pneumothorax
  - F/s/o vasculitis
  - Atypical radiographic picture
  - Unexplained pulmonary HTN
  - Unexplained cardiomegaly
  - Rapid progression or new onset rapid deterioration
- Relative contraindications to this procedure include:
  - Serious cardiovascular disease
  - Roentgenographic evidence of diffuse, end-stage disease, eg, "honeycombing"
  - Severe pulmonary dysfunction or other major operative risks (especially in the elderly population)
  - High likelihood that an adequate sized biopsy from multiple sites, usually from two lobes, will not be obtained [31]

ILD- HISTOPATHOLOGY

- UIP – Honey combing fibrosis with prominent fibroblastic foci
- NSIP – Variable interstitial fibrosis and inflammation
- DIP – Intra-alveolar macrophage accumulation
- RB-ILD – Peri-bronchiolar macrophage accumulation
- AIP(DAD) – Diffuse alveolar damage with hyaline formation
- LIP – Infiltration of interstitium and alveolar spaces of lung by lymphocytes, plasma cells and lymphoreticular elements