The Idiopathic Interstitial Pneumonias

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General Comments About ILD

• Consultation with the radiologist is extremely valuable in making a diagnosis of ILD
• Consultation with the clinician is usually helpful—it generally limits the differential diagnosis
• It’s very difficult to diagnose ILD without clinical and radiologic information?
• Some cases of ILD defy exact classification – consider collagen vascular diseases and drug reactions in this situation

The “idiopathic” Interstitial Pneumonia Problem

• There are a number of entities referred to as idiopathic interstitial pneumonias
• Some are not idiopathic (RBILD, DIP)
• Some are not really interstitial pneumonias (AIP)
• The formal classifications tend to hide the real prognostic features
• The term “idiopathic interstitial pneumonia” is actually useless
Liebow Classification of Idiopathic Interstitial Pneumonias-1970s

Usual interstitial pneumonia (UIP)
Bronchiolitis Obliterans with Interstitial Pneumonia (BIP)
Desquamative Interstitial Pneumonia (DIP)
Lymphocytic Interstitial Pneumonia (LIP)
Giant Cell Interstitial Pneumonia (GIP)

Classification of Idiopathic Interstitial Pneumonias
(ATS/ERS Consensus Classification: Amer J Respir Crit Care Med 2002; 165: 277)

- Histologic Pattern
  • Usual interstitial pneumonia
  • Nonspecific interstitial pneumonia
  • Organizing pneumonia (OP)
  • Diffuse alveolar damage
  • Respiratory bronchiolitis
  • Desquamative interstitial pneumonia

- Clinical-Radiol-Pathol Diagnosis
  • Idiopathic pulmonary fibrosis
  • Nonspecific interstitial pneumonia (NSIP)
  • Cryptogenic organizing pneumonia (COP, BOOP)
  • Acute Interstitial pneumonia
  • RB Interstitial lung disease
  • Desquamative interstitial pneumonia (DIP)

General Morphologic Approach to Chronic Interstitial Lung Disease

- Is this is a malignancy; eg lymphangitic ca, lymphoma?
- Is this an infection (PCP, CMV) ?
- Is this an interstitial lung disease with a defined specific feature; eg, sarcoid?
- Is this a form of idiopathic chronic interstitial pneumonia?
- Is this a localized artifact (scar, edge of another lesion, etc)?
  - ILD are diffuse conditions by definition
- Is this a drug reaction or a collagen vascular disease?
Diseases Associated with a Morphologic Picture of UIP

- Idiopathic UIP
  - Equivalent to clinical “Idiopathic Pulmonary Fibrosis”
- Collagen vascular disease
  - Esp RA and scleroderma
- Drug reactions
  - Amiodarone, ?Nitrofurantoin, ?Chemotherapeutics
- Familial UIP
  - UIP in 2 more more family members
  - Surfactant C processing deficiency
- Some cases of chronic hypersensitivity pneumonitis
- Some pneumoconioses such as asbestosis (but usually not great microscopic mimics)

Clinical Features of UIP

- Disease of middle-aged and elderly
  - Incidence as cases/million (Coultas et al 1994)
  - Age Males Females
  - 45-54 22 40
  - >75 1530 900
- Think twice before making this diagnosis in patients under age 50
  - Exception: Patients with collagen vascular disease

- Typically presents with a history of insidious onset of shortness of breath
- Shortness of breath increases over a period of many months to years
- Velcro rales on inspiration
- Clubbing in as many as 50% of cases
Usual Interstitial Pneumonia

Macroscopic honeycombing

Courtesy Dr. N. Müller
Microscopic Features of UIP

- Patchy pattern of interstitial inflammation & fibrosis mixed with normal parenchyma
- Honeycombed areas or solid scars (architectural distortion)
- Tends to be worse in periphery of lobule
- Scattered fibroblast foci (small tufts of granulation tissue applied to alveolar walls)
- Interstitial inflammation minimal except in honeycombed foci
- Airspace macrophages minimal except in honeycombed foci
- Temporal and morphologic heterogeneity
Fibroblast Foci: Progressive organization leads to "interstitial fibrosis."
Separation of BOOP from Fibroblast Foci

- **BOOP**
  - Granulation tissue clearly in airspace or RB
  - Granulation tissue separate from surrounding lung
  - No fibrosis in surrounding lung (but often chronic interstitial inflammation)
  - BOOP foci usually not covered by epithelium
  - Usually much more numerous than fibroblast foci

- **Fibroblast foci**
  - Granulation tissue always attached to underlying lung
  - Underlying lung usually densely fibrotic
  - Granulation tissue oriented parallel to underlying lung
  - Fibroblast foci frequently covered by epithelium

Other Conditions that May, At Least Focally, Produce a Pathologic Picture More or Less Resembling UIP

- Fibrotic forms of hypersensitivity pneumonitis [look for giant cells/granulomas]
- Burnt out sarcoid, eosinophilic granuloma
- Burnt out TB or fungal infection
- Chronic aspiration (look for foreign body giant cells/lipid droplets)
- Fibrotic foci of chronic eosinophilic pneumonia
- Organized & honeycombed ARDS
- Old radiation injury
- Old drug injury (chemotherapeutic agents)
- Old local scars
- Fibrotic foci around bronchiectasis
Dealing with Pathologic UIP Mimics

- *Clinical and radiologic information will sort out most cases of UIP from mimics*
- Chronic (fibrotic) hypersensitivity pneumonitis may not be separable from UIP on radiologic or pathologic features
  - But the prognosis is similarly poor for both (Churg et al: AJSP 2010)
Complications/Causes of Death in UIP

- Acute exacerbation - acute lung injury superimposed on UIP
  - Cause of death in ~50% of cases? *
  - But not all acute exacerbations are fatal**
- Carcinoma of lung (approx 10 fold risk)
- Pulmonary hypertension/cor pulmonale
  - May be associated with acute exacerbations (Judge et al: 2012)
- Respiratory failure secondary to progressive fibrosis


Acute Exacerbation of UIP

- Rapid development of respiratory failure in a patient with UIP (occasionally NSIP)
- Extensive ground-glass opacities or consolidation on HRCT
- Not caused by heart failure or infection
- Pathologic picture of UIP + DAD or UIP + OP
  - Sometimes hard to see the underlying fibrosis!

(Churg et al AJSP 2007; Churg et al Histopathol 2011)
Acute Exacerbation of UIP

- Incidence uncertain
  - Retrospective review of 461 cases showed a 1 year incidence of 14% and a 3 year incidence of 21% (Song et al. Eur Respir J 2010)
  - Mortality 50 to 70%, but not all acute exacerbations are fatal (Martinez et al. Ann Int Med 2006; Churg et al. Am J Surg Pathol 2007)
- NB: Acute exacerbation can be the initial presentation of some cases of UIP

Causes of Diffuse Alveolar Damage Diagnosed on Surgical Lung Biopsy*

- Series of 58 patients
- Infections 22%
- Complications of transplant 17%
- Collagen vascular disease 16%
- Acute exacerbation of fibrotic ILD 12%
- Drugs 10%
- Radiation 2%
- Acute interstitial pneumonia 21%

*Parambil: Chest 2007
Acute Exacerbation of UIP
If you are suspicious of an underlying fibrotic interstitial pneumonia but can’t see anything definite, ask radiology—they may be able to discern fibrosis under the acute process or have a prior film on which the diagnosis is obvious.
Treatment of UIP

- **Things that don’t work** (Raghu et al: Am J Respir Crit Care Med 2011)
  - Steroids with/without Cyclophosphamide
  - Cyclosporine A
  - Interferon-γ
  - Bosentan (endothelin receptor antagonist)
  - Imatinib (tyrosine kinase inhibitor)
  - Colchicine
  - Etanercept (anti-TNF therapy)

- **Things that might be of benefit but not established**
  - Perfenidone (anti-fibrotic agent) (Lancet 2011; 377: 1760)
  - Anti-reflux therapy
  - N-acetyl cysteine (anti-oxidant)

- **Transplantation** (for younger patients)

Survival in UIP (compared to NSIP)

![Graph showing survival rates for UIP and NSIP over years following diagnosis](image-url)
When dealing with a putative case of idiopathic interstitial pneumonia, separation of UIP from everything else is the most important role of pathologic diagnosis.
How good is the radiologic diagnosis of UIP and when does it substitute for biopsy?

- With a classic pattern on CT and an experienced radiologist, the positive predictive value of CT is 96%.

The Pathologist, the Radiologist, and UIP

• A classical HRCT for UIP is very helpful (>95% specificity)
• However, at least 50% of UIP cases do not show a classic radiographic HRCT pattern – These cases have slower progression
• Pathology trumps radiology: If it’s UIP on biopsy, diagnose UIP

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Nonspecific Interstitial Pneumonia (NSIP)

• A name applied to a form of idiopathic interstitial pneumonia typically characterized by ground glass infiltrates/reticulation on HRCT and linear interstitial inflammation/fibrosis on biopsy
• To some extent an exclusionary diagnosis
• Some cases by morphology and behavior represent hypersensitivity pneumonitis
• Strong association with collagen vascular disease
• Drug reactions can produce an NSIP picture
• Some cases may be UIP with an unlucky sample
• Many cases have a good prognosis
NSIP - Clinical Features

- Usually occurs in middle aged adults (avg age about 50) but cases have been reported in children
- Average duration of symptoms before presentation 14 mo (3 mo to 4 years in reported series)
- Typical complaint is shortness of breath, but systemic complaints (fever, wt loss) may be present
- Restrictive disease with crackles
- Plain films show interstitial markings, usually lower zone
- HRCT shows patchy lower zone ground glass attenuation +/- reticulation and minimal or absent honeycombing

Cellular NSIP: Ground Glass Opacities

Fibrotic NSIP: Ground Glass Opacities + Reticulation
Pathologic Features of Nonspecific Interstitial Pneumonia (NSIP)

- Tends to be morphologically and temporally homogeneous
- May show only chronic interstitial inflammation in a homogenous linear pattern
- May show fibrosis in a homogeneous linear pattern
- Small areas of OP may be present
- Lymphoid nodules may be present (typically in collagen vascular disease case)
- In general interstitial inflammation (if present) is considerably more intense than in UIP
- Usually absence of architectural distortion/honeycombing
Nitrofurantoin toxicity as cellular NSIP pattern

Fibrotic NSIP with slight inhomogeneity
Homogeneous Linear Fibrosis +/- Inflammation ("NSIP" Pattern): Differential Diagnosis

- Some cases of hypersensitivity pneumonitis [can be identical]
- Old chronic eosinophilic pneumonia
- Some areas of burnt out eosinophilic granuloma
- Old fibrotic forms of ARDS
- Drug reactions
- Edge of BOOP lesions
- Chronic pulmonary hemorrhage
- Long standing DIP
- Collagen vascular disease (= "NSIP")
- Focally in UIP!
- Idiopathic NSIP (exclusionary)

Nonspecific Interstitial Pneumonitis as the Sole Histologic Expression of Hypersensitivity Pneumonitis

Vourlekis JS, Schwarz MI, Cool CD, Tuder RM, King TE, Brown KK.

Homogeneous Linear Fibrosis +/- Inflammation ("NSIP" Pattern): Differential Diagnosis

- Some cases of hypersensitivity pneumonitis [can be identical]
- Old chronic eosinophilic pneumonia
- Some areas of burnt out eosinophilic granuloma
- Old fibrotic forms of ARDS
- Drug-induced NSIP-like reactions are common: remember that NSIP is a diffuse disease
- Chronic pulmonary hemorrhage
- Long standing DIP
- Collagen vascular disease (= "NSIP")
- Focally in UIP!
- Idiopathic NSIP (exclusionary)

Local NSIP-like reactions are common: remember that NSIP is a diffuse disease

Edge of BOOP lesion: not NSIP

Ask radiology what the CT scan looks like
NSIP Areas In UIP
(Katzenstein et al: AJSP 2002; 26: 1567-1577)

- Found in 12 of 15 biopsy specimens
- Usually <10% of abnormal areas
- Typical UIP patchy involvement with architectural distortion (honeycombing or solid scars) present in other areas
- Fibroblast foci (more typical of UIP) present in other areas
- If areas that look like UIP are present, diagnosis is probably UIP
Discordance in ILD Biopsies  
(Monaghan Chest 2004)

- N = 64 patients with ILD ?UIP and 2 biopsies performed at time of VATS
- 25/64 UIP/UIP ("concordant")
- 31/64 NSIP/NSIP ("concordant")
- 8/64 NSIP/UIP ("discordant")
- The discordant NSIP/UIP cases had the same survival as the concordant UIP/UIP cases (much worse than NSIP/NSIP), indicating that UIP trumps NSIP in regard to prognosis

Survival in Idiopathic Interstitial Pneumonias


Important Things to Put in the Diagnosis Line for NSIP

- Presence or absence of fibrosis
  - Cellular, fibrotic or mixed
  - Evidence of collagen vascular disease
- I include the major differential diagnoses in a comment
  - Collagen vascular disease
  - Hypersensitivity pneumonitis
  - Drug reactions
- Remember that NSIP is really a reaction pattern
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Desquamative Interstitial Pneumonia (DIP) and Respiratory Bronchiolitis with Interstitial Lung Disease (RBILD)

- Smoking-related forms of ILD
  - Smoking history 100% of patients with RBILD
  - Smoking history 60 to 90% of patients with DIP
- Other putative causes
  - Fumes
  - Dusts
  - Drugs
  - CVD
  - No obvious exposures

Relationship of RBILD and DIP

Interstitial inflammation (incl eosinophils/fibrosis)
**DIP/RBILD Clinical Features**

- Age: RBILD on average younger than DIP
- Presenting symptoms
  - SOB - most patients
  - Cough - many patients
  - May be asymptomatic
- Physical signs
  - Inspiratory crackles ~ 50%
  - Clubbing ~ 25%
- PFT
  - Low DL_{CO} most consistent finding
  - May have restrictive or obstructive or no abnl
- Based on 35 patients reported by Ryu et al: Chest 2005

**RB/RBILD Morphology**

- RBILD (and RB = smoker’s respiratory bronchiolitis)
  - Pigmented macrophages (smoker’s macrophages) in a more or less bronchiocentric pattern
    - But smoker’s macrophages can be present in small numbers in a wide distribution
  - Mild fibrosis of walls of respiratory bronchioles
  - Sometimes fibrosis of alveolar walls away from bronchioles
- NB: There are no clear morphologic differences between RB (smoker’s respiratory bronchiolitis) and RBILD
  - The differences are in the imaging/clinical findings
Smoker’s Respiratory Bronchiolitis (RB) vs RBILD *

- Respiratory bronchiolitis (RB) present in almost all smokers
- RBILD by definition must have evidence of an interstitial lung disease
  - Restrictive PFT or reticulation on CT
  - Or diffusing capacity disproportionately reduced
  - Only RB/RBILD morphology on biopsy
  - No other cause of an ILD!!!! If another defined interstitial lung disease is present, don’t diagnose RBILD
- Otherwise RB by itself is a part of cigarette smoke-induced airflow obstruction

*Churg et al.: Arch Pathol Lab Med 2010

If no clinical evidence of ILD, then this is respiratory bronchiolitis (RB), a part of COPD. This is a very common lesion in smokers
If clinical evidence of an ILD and no other cause in biopsy then this is RBILD, an uncommon lesion

RB/RBILD with focal marked fibrosis ("smoking-related interstitial fibrosis")
Pathologic Features of Desquamative Interstitial Pneumonia (DIP)

- Extremely homogeneous process over large area
- Airspaces filled by (pigmented) macrophages
- Mild interstitial inflammatory infiltrates
- Lymphoid nodules common
- Small numbers of eosinophils
- Interstitial fibrosis may be present, but usually linear without architectural distortion
- Individual fields indistinguishable from individual fields of RB/RBILD
- Longstanding cases may look like fibrotic NSIP
Processes that May Mimic DIP

- Macrophage collections around lesions of eosinophilic granuloma (Langerhans cell histiocytosis) and sometimes around tumors
- Drug reactions, especially to Amiodarone, statins
- Obstructive pneumonias with collections of foamy macrophages
- Rhodococcus and Mycobacterium avium infections in immunocompromised hosts
- Chronic eosinophilic pneumonia
- Focal microscopic finding in many conditions (for ex, NSIP)–not a diagnostic entity in this setting
Treatment/Survival in RBILD/DIP

- Treatments: Steroids, smoking cessation
- Outcomes
  - Carrington 78 RBILD 72% (9 yrs)
  - Yousem 89 DIP 68%
  - Ryu 05 DIP 74%
  - Portnoy 07 DIP 96%
  - Kawabata 12 DIP 78% (10 yrs)**

**Only 1 DOD but 36% honeycombing
* 1 of 23 patients developed progressive ILD. Most patients did not improve but many stabilized

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