Why?

- Much of interstitial lung disease biopsies are being supplanted by HRCT analysis and clinical diagnoses:
  - UIP, HP, CTD
- The biopsies that are being performed are the strange cases, and will likely be more difficult.

Disclosure Statement

Relevant financial relationships with a commercial interest:
- Boehringer Ingelheim, speaker

Overview

- Normal lung anatomy
- Patterns of fibrosis
- Some side trips along the way to discuss
  - Acute lung injury
  - Granulomas
Normal Lung

- The lung is divided into numerous lobular units that have a characteristic appearance.
  - Arteries run with airways.
  - Veins present in interlobular septa.
  - Lymphatics in bronchovascular bundles, interlobular septa, and pleura.

The Pulmonary Lobule
**Pattern of Fibrosis**

- The distribution of the fibrosis will often correlate with the nature of the injury.
- Bronchiolocentric fibrosis – tends to occur in diseases with inhalation injury (HP, RB, fume) or bronchiolar inflammation (CTD)
- NSIP – tends to occur in diseases with diffuse alveolar inflammation (autoimmune CTD, drug reaction, HP)
- UIP – odd peripheral distribution pattern. Possibly related to aberrant senescence with most distal cells either more predisposed to stretch injury, or least likely to be replenished.
Bronchiolocentric Fibrosis

- Look for lace-like central regions (fireworks) of peribronchiolar metaplasia
- Think about inhaled diseases (HP, RB, fume inhalation injury) and diseases with small airway inflammation (aCTD)
Case 1

- 49-year-old woman with shortness of breath for 6 months.
- CT shows centrilobular consolidation and GGO
**Case 1 - Diagnosis**

- Giant cell interstitial pneumonia
- Hard metal pneumoconiosis
- Exposure to tungsten
  - Sawblade sharpener, diamond polisher, foundry worker
  - China cases
  - Vape pen?

**Bronchiolocentric Fibrosis**

- Recognize by central changes

- Build your differential based on inhalation versus airway inflammation
  - Smoking (RB, PLCH)
  - Inhalation/aspiration (fume or food)
  - Occupational (pneumoconiosis, “popcorn lung”)
  - Some systemic diseases (CTD, IBD) due to airway inflammation
  - Some idiopathic cases (fibrosis, OB, DPB)

**Nonspecific Interstitial Pneumonia (NSIP)**

- Diffuse alveolar septal thickening by either inflammation (cellular NSIP) or fibrosis (NSIP-fibrosis)

- Can be variable, but should show fibrous thickening of the alveolar septa in peribronchiolar, subpleural, and midzones of the lobule.
NSIP Pattern

- Look for variable but diffuse alveolar septal thickening (dusty cobweb) by fibrosis or inflammation
- Look for additional clues to help decide the differential (lymphoid aggregates, granulomas, pleuritis, vessel thickening).

If my pathologist tells me the biopsy shows NSIP, then my job has only just begun.
First Side-Trip: Diffuse alveolar damage

- Damage to epithelium (pneumocyte) and endothelium (alveolar capillary)
- Septal edema, septal inflammation
- Airspace fluid, protein, fibrin
- Formation of hyaline membranes

Clues for DAD

- A compatible clinical history
- Diffuse alveolar septal thickening or effacement by collapse, edema, and alveolar filling
- Hyaline membranes
- Distal airway squamous metaplasia

Case 2

- 44-year-old woman with relatively abrupt onset of shortness of breath following trip to Ireland.
- Treated for pneumonia. Mild improvement, but still dyspneic after one year.
Second Side-Trip: Granulomas

- Finding granulomas on a biopsy can help make several diagnoses, so it is important to recognize what they look like
- Rounded aggregates of histiocytes (tissue macrophages) often with multinucleate giant cells

Granuloma – Soft Findings

- Tightly packed cells, rounded, coalescing, present along lymphatic routes, lymphocytes exclude the interior = sarcoidosis
- Tightly packed, rounded, singletons, random or bronchiolo-centric, lymphocytes in interior = MAC, hot-tub lung
- Loose, formed of only a few macrophages and giant cells, may show intracytoplasmic cholesterol clefts, bronchiolo-centric often = HP
- Associated with neutrophils, big floppy giant cells = aspiration
Hot-tub lung (M. avium)

Hypersensitivity Pneumonia
H.P. - Micro

- “Triad of four things”
  - 1a: Interstitial chronic inflammation
  - 1b: Bronchiolocentric inflammation
  - 2: Poorly formed granulomas
  - 3: Foci of organizing pneumonia

Hypersensitivity Pneumonia

- Cases we have observed:
  - Feathers: Pets, Farm animal, Duvet, Pillow, Jacket.
  - Molds: Work freezer, Man-Cave, Sleep number mattress, Hay, Orchid bark
  - Mycobacteria: Indoor spa, shower
  - Machine oil
  - ? Central valley: Almond dust?

Courtesy of Rick Webb, MD
Back to Case 2

- Diagnosed with cellular and granulomatous interstitial pneumonia.
- Follow-up:
  - 6 years later (including 5 year post-op mark)
  - 8 years later…
Case 2

- Cellular NSIP with granulomas progressing to fibrotic NSIP, transplanted, then recurred in the donor lung.
- Hot-tub lung (M. avium)

Nonspecific interstitial pneumonia (NSIP)

- Recognize by involvement of all zones of lobule without significant architectural destruction
- Build your differential based on systemic (or diffuse) inflammation:
  - Connective tissue disease
  - Drug reaction
  - Hypersensitivity pneumonia (with br-centric accentuation)
- Modify Based on Other features
  - Lymphoid aggregates – CTD, smoking, drug
  - Granulomas – HP, rare CTD, rare drug, infection

UIP Pattern

- Fibrosis beginning at the periphery of the lobule
- Temporal and spatial heterogeneity
- Temporal (“HORN”)
  - Honeycombing, old (dense collagen) fibrosis, recent (fibroblast foci) fibrosis, and normal
- Spatial – worse subpleural, paraseptal, and basilar
The “Tip Test”

- Since UIP shows peripheral lobular accentuation of fibrosis, the very tip of the surgical biopsy is often obliterated by fibrosis (often with overlying fatty metaplasia of the pleura)

- NSIP tends to show normal alveolar architecture (with thickened septa) at the tip of the biopsy.
Case 3

- 65-year-old man with 2-year history of shortness of breath. Started with feeling wheezy during exercise, progressed to decreased exercise tolerance and most recently has had 2-3 months of dry cough.
- CT shows subpleural reticulation with honeycombing.
- No exposures for HP. Serologies negative.
Case 3

- Upon admission from clinic, he was found to have had increasing joint pain for the last three weeks (mirroring the worsening shortness of breath).
- Anti-CCP and RF positive.
- RA-ILD
Case 4

- 56-year-old woman with several years history of dry cough and CT scan with “reticulation”. Her mom died of pulmonary fibrosis in her early 60’s due to “lupus”.

Case 4

- Patient’s blood sent to UT Southwestern to Dr. Christine K. Garcia.
- TERC mutation
- Familial IPF (although at least partially not “idiopathic”)

UIP Pattern

- When there is “true” temporal heterogeneity, the diagnosis is almost certain
- Use the “Tip Test”
- Build differential based on abnormal senescence and injury patterns
- Rare cases of HP, CTD may show UIP pattern
  - Look for central scarring and granulomas in HP
  - Look for increased lymphoid aggregates and lack of normal (NSIP instead) in CTD

Take Home Message

- Differing patterns of fibrosis can help to guide the differential diagnosis.
- Acute lung injury can mimic chronic disease, so correlating any lung biopsy with clinical history and CT findings is important.
- Granulomas, while histologically non-specific, also have different appearances that can help to guide the differential diagnosis.