“The delivery of health care has proceeded for decades with a blind spot: Diagnostic errors – inaccurate or delayed diagnoses – persist throughout all settings of care and continue to harm an unacceptable number of patients.”

“the committee concluded that most people will experience at least one diagnostic error in their lifetime, sometimes with devastating consequences.”
Histopathologic Diagnosis in Diffuse Lung Disease: An Ailing Gold Standard

“The recent view that a final diagnosis should be made by *consensus* between histopathologist, radiologist, and clinician is a radical departure from the diagnostic thinking of the late twentieth century.”

†Athol Wells. Am J Respir Crit Care Med 2004; 170: 828
Case 1

RLL wedge (10.2 x 3.2 x 2.6 cms) from 79-year-old man for frozen section

“ill-defined, tan-grey, mottled tumor, 1.1 x 0.9 x 0.9 cm . . . 0.2 cm away from the pleura and 0.3 cm away from the margin of resection”

clinical history: “Lung mass”

frozen section diagnosis: Adenocarcinoma
79-year-old man with “idiopathic pulmonary fibrosis” diagnosed 5 months prior to referral
4 month history of shortness of breath & diffuse radiological abnormalities

Persistent interstitial lung disease characterized predominantly by peripheral basilar abnormalities that largely consist of interlobular septal thickening and traction bronchiectasis. There may be mild ground glass opacity, but honeycombing is not an important feature of abnormality. Between 6/9/2006 and 9/22/2006 there is not a major change.

a somewhat bilobed nodule in the superior segment of right lower lobe, not clearly changed in the interval. The larger more cephalad and posterior component measures 1.5 cm in size.
past medical history
3.5 years status post CABG
13 pack-years of cigarette smoking
pulmonary function studies
mild restriction (FVC 68% of predicted value)
$D_{LCO}$ 55% of predicted value

PET scan
Right lower lobe ill-defined nodular opacity with FDG avidity comparable to the mediastinal blood pool, suggesting an inflammatory process. However low-grade neoplastic tumor such as bronchoalveolar carcinoma cannot be completely excluded and followup chest CT is recommended.
Follow-up CT (4 months)
1. Stable basal predominant interstitial lung disease with interlobular septal thickening, mild traction bronchiectasis, and minimal ground glass opacity. The appearance favors nonspecific interstitial pneumonia.
2. Growing bilobed nodule in superior segment of right lower lobe compared with 9/22/2006. Both components of this bilobed nodule are larger, and are in the 2 cm size range. Neoplasm is a significant concern.

Completion lobectomy
“The cut surface is a red-tan lung parenchyma. No lesions are noted. Along one of the staple lines an area of hemorrhage is noted. No other abnormalities are present.”

Case 1 – Diagnosis
Adenocarcinoma Arising In Usual Interstitial Pneumonia
Usual Interstitial Pneumonia (UIP)  
Histologic Criteria  

- fibrosis  
- heterogeneity (variegated pattern)  
  - geographic heterogeneity  
  - temporal heterogeneity

“patchwork”
Usual Interstitial Pneumonia (UIP)
Histologic Criteria

- fibrosis
- heterogeneity (variegated pattern)
  - geographic heterogeneity
  - temporal heterogeneity
- architectural distortion
  - honeycomb change
  - fibrotic scarring

Usual Interstitial Pneumonia
Peripheral Honeycomb Change
Usual Interstitial Pneumonia (UIP) Histologic Criteria

- fibrosis
- heterogeneity (variegated pattern)
  - geographic heterogeneity
  - temporal heterogeneity
- architectural distortion
  - honeycomb change
  - fibrotic scarring
- peripheral/subpleural accentuation

Usual Interstitial Pneumonia/IPF Lung Cancer in 24 Patients

UIP initially diagnosed in only 4 (16.7%) of 24 surgical patients with UIP on re-review

†Schmidt et al. 2010 USCAP abstract #1842
Usual Interstitial Pneumonia/IPF
Lung Cancer – Pathological Findings

- peripheral
- squamous cell carcinoma >> adenocarcinoma

Case 2

- 69-year-old woman
- asthma x 6 yrs
  non-productive cough x 2 yrs
- increasing breathlessness with vigorous activity or golfing
- symptoms improved during previous winter (attributed to inhaler)
- retired teacher
- no pets
- spends winters in Texas
- HRCT
  - ground glass opacities
  - traction bronchiectasis
  - “minimal honeycombing peripherally in the lower lobes”

VATS wedge biopsy of RLL & RML
“R/O IPF”

Case 2 – Diagnosis
Hypersensitivity Pneumonia
Hypersensitivity Pneumonia
Pathology

chronic interstitial pneumonia
– “NSIP-like”, “UIP-like”
– bronchiolocentric

chronic bronchiolitis
– OP (“BOOP”) in 50%

non-necrotizing granulomatous inflammation (~70-80%)
– isolated multinucleated giant cells
peribronchiolar metaplasia

Chronic HP vs UIP
Autopsy Findings†

peribronchiolar metaplasia

non-necrotizing granulomatous inflammation

†Akashi et al. Am J Clin Pathol 2009; 131: 405
Hypersensitivity Pneumonia
Impact of Biopsy Fibrosis on Outcome†

**fibrosis** =
- alveolar septal expansion by mature collagen in ≥ 5% of surface area on single slide
- honeycomb change

![Image of fibrosis](image)

\[ n = 72 \]

46 = “fibrotic” HSP
26 = “nonfibrotic” HSP


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**Hypersensitivity Pneumonia**
**Impact of Biopsy Fibrosis on Outcome†**

- 2 (7.7%) respiratory deaths in nonfibrotic group
- 14 (30.5%) respiratory deaths in fibrotic group
- dyspnea score and fibrosis the only statistically important predictors of mortality

![Graph showing survival](image)

Kevin [Brown],

Have been pondering a question that comes up regularly in consultations and wasn’t sure who to ask, and it occurred to me that you’re the perfect consultant for this question! I say this because of your expertise and experience with both IPF and HP, and your thoughtful insights regarding the ways in which clinicians and pathologists communicate.

My question pertains to surgical lung biopsies that have areas indistinguishable from UIP but other clues that the etiology is almost certainly HP. In this case . . . No question in my mind that she, 1) has chronic HP, and 2) is at a late fibrotic stage in her disease for which distinction from UIP/IPF may not be terribly meaningful.

Have struggled with how to say this in path reports over the last couple of years and have been inconsistent. Menu of options that I think I’ve exercised include . . .

My question to you as a practitioner is, do any of these make more sense to you than another. If not, how would you PREFER that biopsy results be reported on such a patient?

Jeff -

I fully acknowledge my bias here. Others may assuredly feel differently.

You know my take, I am not asking the pathologists to give me the diagnosis (I view this differently than cancer). What I want to know is the pattern and features that have a prognostic impact with or without therapy. This is probably more in depth than many pulmonary folks want to go, but there is probably a middle ground.

My preference would be something along the lines of

"fibrotic hypersensitivity pneumonitis with UIP-like features".

To me this gives me etiologic and therapeutic information, the HP, and prognostic information, the fibrosis. The term chronic doesn’t do much for me because we and others have found no relationship between duration of exposure and pathologic features except maybe for the neutrophilic acute HP. The UIP pattern portion is probably useful as a prognostic term because most recognize that the pattern is associated with a bad outcome, and therefore may capture the prognostic information better than "fibrotic HP" alone for most folks.
Case 2 – Diagnosis

fibrotic hypersensitivity pneumonia with *UIP-like* features

Case 3

• 29-year-old man
• “suspected of having Langerhans cell histiocytosis (LCH)”
• previous TBBx = “organizing pneumonia”
Langerhans Cell Histiocytosis

PULMONARY LCH
Clinical Features

• young adults (3rd - 4th decade)
• cigarette smokers
• 75% symptomatic (cough, DOE, chest pain)
• CxR: diffuse interstitial infiltrates, upper lobe predominance
Challenges in Pulmonary Pathology

Case 4

- 48-year-old man
Case 4
Challenges in Pulmonary Pathology

• 48-year-old man
• sudden onset of chest pain after climbing stairs
• chest x-ray elsewhere - pneumothorax
• CT scan
  – diffuse, bilateral cystic change
  – unilateral adrenal mass

“Multiple thin-walled pulmonary air cysts are seen throughout both lungs. These pulmonary cysts could represent Langerhans cell histiocytosis. Lymphangioleiomyomatosis would be unlikely because the patient is male, and lymphangioleiomyomatosis is almost always seen in female patients.”
CSP Video Tutorial - Myers

Case 4

Challenges in Pulmonary Pathology

- bx/resection adrenal mass = adenoma with extramedullary hematopoiesis
- 1 week post-op – recurrent chest pain and shortness of breath
- chest x-ray – recurrent pneumothorax
- pleurodesis and lung biopsy

Case 4 – Diagnosis

Lymphangioleiomyomatosis

Does LAM ever REALLY occur in men?

... real, honest-to-goodness, XY males?
other stigmata of TSC
• facial angiofibromas
• renal angiomyolipoma

TSC2 mutation

2 subsequent reports of LAM in men with probable or definite TSC
- Kim et al. Pathol Int 2003; 53: 231

Case Report

Pulmonary Lymphangioleiomyomatosis in a Karyotypically Normal Man without Tuberous Sclerosis Complex

Mario Schiariti, Valterio Di Scipio#, Paolo Cerilli#, Alberto Cavazz0, Andrea Fabiani#, Marco Barbieri#, Alessandro Biasi#?, Annamaria Almecig#, Robin M. T. Cocker, Walter F. Grigioni#, and Antonia D’Ercole-Crugnola#

Am J Respir Crit Care Med 2007; 176: 96

- 37-year-old man
- left pneumothorax and left lung collapse
- no stigmata of TSC
- negative for TSC1 and TSC2 germline mutations
Case 5 Challenges in Pulmonary Pathology

- 25-year-old woman
- referred for evaluation of lung mass
- PMH
  - asthma
  - discovered to have lung mass about the “size of a quarter” 5 yrs PTA

24.3 mm ≈ 2.5 cm

Case 5 Challenges in Pulmonary Pathology

- shortness of breath 3 yrs PTA
  - CT – mass had enlarged
- weight loss, hemoptysis 1 yr PTA
  - CT – mass had enlarged to ≈ 4 cm
- multiple studies, including percutaneous core needle biopsy,
  “however, as of yet, the etiology of this mass remains elusive.”

FINDINGS:
“There is a round 3.7 x 3.6 cm solid well circumscribed mass located within the medial basilar segment of the left lower lobe with some adjacent ground glass along the medial aspect of the mass, which may represent hemorrhage versus atelectasis. The mass is relatively homogenous in appearance without evidence of intralobesional fat or calcification.”

IMPRESSION:
1. Well-circumscribed central left lower lobe lung mass, measuring 3.7 x 3.6 cm, with no additional pulmonary nodules or enlarged mediastinal nodes.
**PET-CT**

**FINDINGS:**
There is a well-circumscribed mass in the left lower lobe with FDG uptake with a maximum SUV of 5.0. There is a small amount of adjacent atelectasis.

**IMPRESSIONS:**

1. Well demarcated mass in the left lower lobe with mild to moderate FDG uptake. Given the history that this mass has been present for several years and the mild to moderate uptake, **this could represent either a low grade neoplasm, or an infectious or inflammatory process.**

2. No metabolic evidence of metastatic disease.

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**Review of outside needle biopsy**

Lung, left, needle biopsy of lower lobe mass: Probable sclerosing hemangioma.

**History on lobectomy path report**

“Patient with left lower lobe sclerosing hemangioma.”

---

**Sclerosing Pneumocytoma (“Hemangioma”)**
Sclerosing Pneumocytoma
Pathologic Features

- well circumscribed, peripheral, subpleural nodules
  - ~ 3 cms (0.4 to 8.2 cms)

- histologic diversity
  - solid, papillary, sclerotic and hemorrhagic growth patterns
Sclerosing Pneumocytoma
Pathologic Features

• well circumscribed, peripheral, subpleural nodules
  – ~ 3 cms (0.4 to 8.2 cms)

• histologic diversity
  – solid, papillary, sclerotic and hemorrhagic growth patterns

• cytologic diversity
  – rounded, "pale", epithelioid cells
  – dispersed chromatin, small nucleoli
Case 6

- 72-year-old man
- persistent unilateral pleural effusion
- CT scan
  - minimal posterior pleural thickening with calcifications
  - small to moderate pleural effusion
  - small right apical pneumothorax
Malignant Mesothelioma

Differential Diagnosis – Malignant

<table>
<thead>
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<th>Mesothelioma Type</th>
<th>Differential Diagnosis</th>
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Malignant Mesothelioma

Challenges in Pulmonary Pathology

Case 6 – Diagnosis

Malignant Mesothelioma

Differential Diagnosis – Malignant

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</tbody>
</table>
For both epithelial and spindle cell mesothelial processes, **true stromal invasion is the most accurate indicator of malignancy**, but stromal invasion is often difficult to assess, especially in small biopsies.”


“Although both p53 and EMA staining have been proposed as markers of mesothelial malignancy, in our experience they are not helpful for the individual case”


1Chiosea et al. Mod Pathol 2008; 21: 742
Benign vs Malignant Mesothelial Proliferations
Role of 9p21 Homozygous Deletion

FISH-based detection of homozygous P16/CDKN2A deletion would have been helpful in confirming a diagnosis of mesothelioma over reactive mesothelial cells in 12 of 13 sample with positive or suspicious cytology.

Ladanyi. Lung Cancer 2005; 49S1: 95S

Malignant Mesothelioma
Link Between Epidemiology and Practice

“... a history of exposure to asbestos should play no role in diagnosis; diagnosis depends only on the gross, microscopic, and special technique observations, as it does with any other tumor.”