RCPA Small Biopsy Course, Adelaide, March 2019

Respiratory And Cardiac Pathology

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'Small' Biopsies for Lung, Pleura

• How small is 'small'?: for this course, 'small' = any potential case in RCPA Small Biopsy Exam

• Some larger cases included…
General Principles

• Histologic pattern of non-neoplastic disease in lung bx often does not delineate specific disease entity, but rather a stereotypic pattern of tissue injury — for which there may be many causes and associations

• Importance of clinicopathologic correlation

• ALL information should be made available (e.g. HRCT etc)
Biopsy Dx Lung, Pleural Disease

- Diagnostic assessment often architectural (e.g. interstitial pneumonias)
- *Ergo*, the **bigger** the biopsy the **better**
- Small tissue samples often introduce an uncertainty factor
- Clinicopathologic correlation often crucial (e.g. radiology such as HRCT; if bx → NSIP pattern but HRCT → UIP, HRCT takes precedence)
- Value = dependent on experience/expertise of reporting radiologist
Lung Biopsy for Diffuse or Non-Neoplastic Disease

- Clinical circumstances determine work-up
- Immunocompromised patient:
  - Recurrence original disease (e.g. lymphoma-leukaemia)
  - Opportunistic/other infection (e.g. *Pneumocystis*)
  - Toxicity (e.g. anti-cancer drugs)
  - Bone marrow Tx: graft-versus-host disease
  - Something completely different
Immunocompetent Patient

- Biopsy work-up is different
- Different spectrum of disease
- Acute *versus* chronic disease: often chronic in case of interstitial pneumonias
- Clinical data again crucial:
  - Duration symptoms
  - ?Dust inhalation; other occupational exposure
  - Anatomic distribution disease
  - Choice of biopsy
Biopsy Work-up: Diffuse Disease

- Immunity OK
  - FRESH tissue for culture
  - Embed all tissue
  - H&E
  - D-PAS
  - Perls' for iron
  - Elastic-VG
  - Other: e.g. ZN
  - ± IPX: e.g. S100, CD1a for Langerhans' histiocytosis

- Immunity not OK
  - FRESH tissue for culture
  - Embed all tissue
  - H&E
  - Gram
  - D-PAS
  - Ag stains for fungi, *Pneumocystis*
  - Other: e.g. ZN, FF
  - IPX: CMV, *Pneumocystis*
Fibreoptic Bronchial Bx, TBBx

- High diagnostic yield: pathology centred on airways or widespread, and hence likely to be sampled
  - Central tumours
  - Sarcoidosis
  - Lung Tx rejection
  - Infection
  - Tracheobronchial amyloidosis
  - Alveolar proteinosis
Fibreoptic Bronchial Bx, TBBx

- Intermediate to low diagnostic yield: localization to airways absent, inconstant, fortuitous, or changes are non-specific and dx restricted by small tissue sample
  - Peripheral nodules
  - Langerhans' cell histiocytosis
  - Interstitial pneumonias*
  - Pneumoconioses*
  - Lymphoid infiltrates
  - Vasculitis syndromes
  - LAM: now a clinical/radiologic dx
Core Biopsy of Lung, Pleura

- Peripheral/pleural mass lesions
- May allow dx of multifocal non-neoplastic lesions such as BOOP
- Correlate with clinical and radiologic findings
- Diagnostic limitations imposed by small amount of tissue sampled
- In general, unsuitable for dx diffuse interstitial disease
Wedge Biopsy Lung (VAT, Open)

• Larger tissue sample than TBBx, more reliable for dx diffuse interstitial disease of any type
• Selection site(s) for bx
  – Correlate with radiology
  – Avoid areas of honeycomb change
• Fresh tissue for microbiology
• Inflation fixation
  – Pathologist or surgeon
  – Or: shake fresh tissue in formalin (also TBBx)
Lung Bx: Initial Checklist

• Why was bx taken?
• Any pre-bx Rx that could modify pathology?
• Recognize artefact such as compression and operative versus genuine haemorrhage, and incidental findings (e.g. minute meningothelioid nodules)
• What is anatomic distribution of disease?
  – Nodular versus non-nodular disease
  – Localisation to components of lung: bronchocentric, vascular, other
Case 1

Bronchial biopsy from a 74-year-old man with a history of chronic cough. Sputum culture had revealed a growth of an atypical mycobacterial species. At bronchoscopy, a plaque-like lesion was noted in a bronchial wall. The patient is said to have been immunocompetent
Case 1

• Diagnosis: Bronchial cryptococcosis
• Cryptococcosis: infection with *C. neoformans*
  – Pulmonary
  – Cerebromeningeal
  – Disseminated
• *C. neoformans*: yeast-like fungus, capsulated or unencapsulated (uncommon; immunocompetent), 2–20 μm, usually 4–6 μm in lung
  – *C. neoformans* var *neoformans* (worldwide, soil)
  – *C. neoformans* var *gattii* (River Red Gum)
Pulmonary Cryptococcosis

- Immunocompetent vs immunoincompetent
  - Defects in T-cell immunity
  - Haematologic malignancies (Hodgkin lymphoma), steroids, diabetes, HIV, sarcoid
- Immunocompetent: nodule/mass (asymptomatic), multifocal nodules, consolidation
- Immunocompromised: diffuse, bilateral, reticular/nodular/miliary lesions or consolidation ± cavitation ± pleural effusion
Case 2

Core biopsy of lung from a 65-year-old woman. No other clinical details were submitted.
Case 2

- **Diagnosis: Organising pneumonia (BOOP/COP)**
- COP = idiopathic bronchiolitis obliterate (organising pneumonia (BOOP))
- COP is preferred terminology but is essentially and implicitly a clinicopathologic diagnosis
- BOOP as histologic dx, either of known cause/association, or unknown (ambiguity)
- **Remember:** dominant feature = organising pneumonia (cf. obliterative bronchiolitis *per se*), and this is perfectly adequate histologic dx
Organising Pneumonia/BOOP

• Confusion!! Histologic pattern = non-specific reaction to wide range lung injuries (including lung infection).

• Ergo, term organising pneumonia arguably better than either BOOP or COP because latter two (may) imply idiopathic BOOP

• Diagnosis of COP/idiopathic BOOP involves exclusion of known causes/associations for organising pneumonia (e.g. absence any micro-organism)
Idiopathic BOOP/COP

• Main histologic findings
  – Patchy organising pneumonia
  – Preservation lung architecture
  – Temporal uniformity

• Negatives
  – Absence chronic interstitial fibrosis (problem: BOOP with interstitial scarring, or DIF with superimposed organising pneumonia??)
  – NO granulomas, neutrophils, abscesses, hyaline membranes/airspace fibrin, vasculitis
Organising Pneumonia/ BOOP

- Associations
  - Idiopathic BOOP/COP
  - Localised organising pneumonia
    - Idiopathic
    - Airway obstruction
    - Nearby other lesion e.g. lung cancer, abscess, infarct
  - Nonbacterial infection (viral, fungal, *Pneumocystis*)
  - Hypersensitivity pneumonitis
  - Vasculitis
  - Haemorrhage/haemosiderosis
  - Radiation
  - Other
Case 3

Wedge biopsy of lung from a 58-year-old man who presented with "multiple small nodules" in his lungs. The patient had a family history of silicosis and had sustained exposure to asbestos for more than 20 years.
Case 3
(Nodular and Cystic Interstitial Disease)

- **Diagnosis:** Pulmonary Langerhans' cell histiocytosis (PLCH)

- **PLCH:** Chronic progressive, indolent or remitting proliferation Langerhans' histiocytes → bilateral peribronchiolar and interstitial nodules, may cavitate

- Usually restricted to lung in adults but can also affect other sites: bone, lymph nodes, skin in 10-15%

- Rare: <2-5% biopsy cases DILD
Langerhans' Cell Histiocytosis

- Virtually all adult cases PLCH are smokers
- ?Role TNF-α, GM-CSF
- ?Role bombesin from NE cells: → recruit macrophages
- ~25% asymptomatic
- Symptoms:
  - Dyspnoea ~40-85%
  - Cough, pleuritic chest pain
  - Pneumothorax 25%
Langerhans' Cell Histiocytosis: Dx

- Clinical/radiologic (esp HRCT)
- Fibreoptic TBBx + BAL: TBBx +ve <50%
- BAL alone: but ↑Langerhans' cells in BALs in other DILDs and in smokers without PLCH
- Wedge biopsy:
  - Multiple nodules, stellate, bronchiolocentric ± interlobular septa and pleura; ± eosinophils; ± cavitation
  - Cellular → fibrotic (scars retain stellate outline) ± honeycombing
  - IPX: S-100, CD1a
  - EM: pentalaminar LCG (Birbeck) granules
Tobacco Smoke-Related Lung Disorders

- 'Chronic bronchitis' and emphysema, and interstitial fibrosis
- Respiratory bronchiolitis (RB)
- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Pulmonary Langerhans' cell histiocytosis
- Lung Cancers:
  - Risk: small cell ca > squamous and large cell ca > adenocarcinoma
Case 4
(Non-nodular Interstitial Disease)

Wedge biopsy of lung from the lingula of 38-year-old man with a clinical background of interstitial lung disease
Case 4

• Diagnosis: Usual interstitial pneumonia (UIP)
• Stereotypic pattern chronic lung disease
• UIP pattern in:
  – Collagen-vascular diseases
  – Drug-induced pneumonia
  – Radiation pneumonitis
  – Familial idiopathic pulmonary fibrosis
  – Hermansky-Pudlak syndrome
  – Asbestosis
  – Hypersensitivity pneumonitis (late-stage)
ATS/ERS Interstitial Diseases

• Chronic
  – Usual interstitial pneumonia (UIP/IPF)
  – Desquamative interstitial pneumonia (DIP)
  – Non-specific interstitial pneumonia (NSIP)
  – Lymphocytic interstitial pneumonia (LIP)

• Acute
  – Organizing pneumonia (BOOP/COP)
  – Diffuse alveolar damage (DAD)
## UIP Versus NSIP

<table>
<thead>
<tr>
<th></th>
<th>UIP</th>
<th>NSIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td>73:37 (2:1)</td>
<td>28:27 (1:1)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>2.5 y</td>
<td>8/12 (1/52 to 8 y)</td>
</tr>
<tr>
<td><strong>Temporality</strong></td>
<td>Variegated</td>
<td>Uniform</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Mild</td>
<td>Mild → marked</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td>Patchy</td>
<td>Diffuse/patchy</td>
</tr>
<tr>
<td><strong>Honeycomb</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Org pneumonia</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Fibroblast foci</strong></td>
<td>Characteristic</td>
<td>Nil/inconspicuous</td>
</tr>
<tr>
<td><strong>5-yr survival</strong></td>
<td>20-45%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>10-yr survival</strong></td>
<td>10-15%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Case 5

"68 yr female. L lower lobe. ?AdenoCa or bronchiolo-alveolar. Non smoker"
Case 5

- Diagnosis: Peripheral invasive adenocarcinoma with lepidic and acinar features + multiple carcinoid tumourlets

- Lesser papillary and micropapillary features

- Quantify each + comment on STAS

- CK7+/CK20-/TTF1+ immunoprofile

- Three carcinoid tumourlets, all <5 mm in diameter, syn+/chr+/CD56+
An approach for testing for predictive biomarkers in patients with lung carcinoma in Australia

**Diagnosis**

- P40+
P40-
- TTF1-
- NSCLC NOS OR favour SCC

**Biomarkers-Approved**

- PDL1
- EGFR
- FISH if IHC +
- ROS1

**Biomarker-Other**

- KRAS
- DNA extraction
- HER2
- BRAF

**MDT input/clinical considerations**

Some done as part of panel e.g. oncofocus

Modified from Manfred Dietel et al. Thorax 2016;71:177-184
Importance of manual microdissection as a prerequisite for reliable and reproducible analyses in molecular pathology.
Molecular Testing: Key Points

- NSCLC is a ‘last resort’ diagnosis
- Molecular testing - generally, >50 cells required
- A negative result may not be informative
Bronchopulmonary NE Lesions

- NE hyperplasias
  - NE cell hyperplasia assoc with fibrosis or carcinoid
  - Diffuse idiopathic pulmonary NE cell hyperplasia (DIPNECH)
- Carcinoid tumourlet (<5 mm by definition)
- Typical carcinoid
- Atypical carcinoid
- Large cell NE carcinoma (LCNEC)
- Small cell carcinoma (SCLCA)
- ?Large cell carcinoma with NE staining on IPX
- ?LCNEC but IPX negative
Criteria for NE Tumours of Lung

• **Typical carcinoid**
  – >5 mm
  – Carcinoid histology
  – <2 mitoses/2 mm² (10 HPF)
  – No necrosis

• **Atypical carcinoid**
  – 2-10 mitoses/2 mm²
  – Or: necrosis

• **Large cell NE carcinoma**
  – NE histology: micro-organoid, palisading
  – 11+ mitoses/2 mm² (median = 70)
  – Cytologic features NSCLCa
  – Positive IPX for 1+ NE markers, or NSG on EM
Key Points

- Things to include in report:
- Distinction between typical vs atypical carcinoid cannot be established from FBBx in most instances
- Entire resected specimen required
Case 6 (16/S07588)

- Right ventricular endomyocardial biopsy from an 87 year old male with restrictive-type cardiomyopathy.

  - H&E stained section
Restrictive Cardiomyopathy

- LV rigid & unyielding; requires high diastolic filling pressure; systolic contraction normal
- Infiltrations
  - Amyloidosis
  - Sarcoidosis
  - Haemachromatosis
  - Idiopathic diffuse fibrosis and end-stage DCM
- Early endomyocardial fibrosis (EMF)
- Endocardial fibroelastosis (EFE)
Case 7 (15/S12597)

- 55 year old male. ? cardiomyopathy
  - H&E stained section
Giant cell myocarditis vs. Sarcoid

- Giant cell myocarditis
  - Rapid clinical course
  - Macroscopic areas of myocardial necrosis
  - Myogenic giant cells at margins of necrosis
  - No granulomata elsewhere

- Sarcoidosis
  - Prolonged course
  - Macroscopic areas of myocardial fibrosis
  - Follicular collections of giant cells
  - Granulomata elsewhere
Sarcoidosis

• multi-organ granulomatous disorder of unknown aetiology which often affects lung, but also other tissues, including lymph nodes, liver, spleen, skin, heart, eye, CNS

• An enigma wrapped in mystery (?related to mycobacterial infection or others)

• Proclivity for Scandinavians, Irish, blacks in US

• ?Role genetics/familial factors
Sarcoidosis

• Diagnosis = demonstration of non-necrotising epithelioid (sarcoidal) granulomas by bx of the most accessible organ by least invasive method

• Dx can be clinical/radiologic only (e.g. Löfgren's syndrome), but definitive dx = CPC correlation

• Hilar ± mediastinal lymph node ± nodular disease on CXR/CT

• Variants:
  – Necrosis (up to 1/3)
  – Endobronchial sarcoidosis
  – Vascular intrusion (up to 50%)
  – Nodular sarcoidosis (<5%)
  – Necrotising sarcoidal granulomatosi (cf. Wegener's)
Sarcoidosis

• Granulomas follow lymphatic pathways
• Exclude TB (ZN, CPC) for anyone from region where TB endemic
• Inclusions
  – Asteroid bodies
  – Schaumann bodies (Ca^{++})
  – Hamazaki-Wesenberg bodies in lymph nodes
Granulomas in lung

- Infections! MUST exclude TB
- Fungi, others
- Sarcoidosis
- FB/aspiration
- Necrotic tumour
- Silicotic nodules
Case 8 (14/S125132)

- 21-year old male - cardiac Tx 4 years ago.?
  - rejection.
  - H&E stained section + VVG stained sections
DIAGNOSIS:

ACUTE REJECTION:
GRADE 3B (MODERATE) 1990 ISHLT
GRADE 3 R (SEVERE) 2004 REVISED ISHLT)
Table 1. ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection\(^b\)

<table>
<thead>
<tr>
<th>Grade 0 R(^a)</th>
<th>No rejection</th>
<th>2004</th>
<th>1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 R, mild</td>
<td>Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage</td>
<td>Grade 1, mild</td>
<td>Focal perivascular and/or interstitial infiltrate without myocyte damage</td>
</tr>
<tr>
<td></td>
<td>A—Focal</td>
<td>B—Diffuse</td>
<td>Diffuse infiltrate without myocyte damage</td>
</tr>
<tr>
<td>Grade 2 R, moderate</td>
<td>Two or more foci of infiltrate with associated myocyte damage</td>
<td>Grade 2 moderate (focal)</td>
<td>One focus of infiltrate with associated myocyte damage</td>
</tr>
<tr>
<td>Grade 3 R, severe</td>
<td>Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis</td>
<td>Grade 3, moderate</td>
<td>Multifocal infiltrate with myocyte damage</td>
</tr>
<tr>
<td></td>
<td>A—Focal</td>
<td>B—Diffuse</td>
<td>Diffuse infiltrate with myocyte damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4, severe</td>
<td>Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage ± vasculitis</td>
</tr>
</tbody>
</table>

\(^a\)Where “R” denotes revised grade to avoid confusion with 1990 scheme.

\(^b\)The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see Table 3).