DIFFICULTIES IN THE PATHOLOGIC DIAGNOSIS OF LUNG CANCER
(Esp. in small biopsies)

Personal Experience
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This talk should mirror the experience of those in the audience!

AREAS OF DIFFICULTY IN THE PATHOLOGIC Dx OF LUNG CANCER
-OBJECTIVES-
1. Knows the areas of difficulty
2. Describe a strategy for dealing with them
3. Review the criteria for the diagnosis of the common forms of lung carcinoma

PROBLEMS IN:

Underdiagnosis: Missing the carcinoma; calling it something less
Overdiagnosis: Calling a metaplastic or reactive process carcinoma; overdiagnosis of indolent cancers
Misdiagnosis: Calling lung carcinoma some other tumor or incorrect classification of lung carcinoma

...All of which are compounded in small biopsies

(General ref: Butnor KJ in Arch Pathol Lab Med 2008;132:1119)
LECTURE OUTLINE

1. Enough to call carcinoma?? (underdiagnosis)
2. Overinterpretation of reactive/metaplastic processes (overdiagnosis)
3. Misdiagnosis
   - Incorrect classification
   - Other misdiagnoses

Emphasis will be primarily on histology in small biopsies rather than cytology.

PATHOLOGIC DIAGNOSIS OF LUNG CANCER: Principles

- WHO 2004 criteria/2011 JTO Adenocarcinoma criteria
- Cyto-histologic correlation
  - Go to your strength (e.g., the smears may have the most cells)
- Share cases
- Keep IPOX in perspective
  - If indeterminate go back to H&E
- Some cases need rebiopsy

1. ? ENOUGH TO CALL CANCER NOT SEEING THE CANCER (Underdiagnosis)

Small specimen/small number of suspicious cells
Bland cytology (esp. mucinous carcinomas)
Obscuring inflammatory changes
  - Necrosis/neutrophilic infiltrate
  - Honeycomb-like
  - Organizing pneumonia/fibrosis-like changes

? ENOUGH TO CALL CANCER

NO!
Bland mucinous epithelium is the key

YES!

And resection showed...

Bland mucinous epithelium is a key feature

? ENOUGH TO CALL CANCER

Was on my own

• Each on of us has a personal threshold- our own personal “gut check”
• Make frequent use of:
  Colleagues
  Additional levels
• Judicious use of immunostains
  Include an H&E with the immunos
ENOUGH TO CALL CANCER

Cellular monotony and mucin production

Shared with colleague who agreed

TIP- Find an internal control*!

Normal bronchiolar epithelium

Key feature: cytologically malignant

Obscuring inflammation present
Inflammation in Lung Cancer

2. OVERDIAGNOSIS OF LUNG CARCINOMA

**Cytologic pitfalls**
- Squamous metaplasia
- Reactive type 2 cells

**Histologic pitfalls**
- Frozen sections
- Type 2 cell hyperplasia
- Metaplasias
- Benign tumors interpreted as carcinoma
- Typical/atypical carcinoid interpreted as small cell carcinoma

**CYTOLOGIC OVERDIAGNOSIS OF LUNG CARCINOMA**

- Granulomatous inflammation
- Lung abscess
- Pneumonias
- Exogenous lipoïd pneumonia
- Bronchial asthma (creola bodies)
- Pulmonary infarction
- Radiation therapy
- Chemotherapy
- Emphysema and chronic bronchitis
- Bronchiectasis
- Autoimmune diseases (esp. RA and pemphigus)
- Chemical pneumonitis

*AFIP Lung Tumor Fascicle, 3rd Series, Fascicle 13

**HISTOLOGIC OVERDIAGNOSIS OF LUNG CARCINOMA**

- Poor fixation, processing, staining
- Overinterpretation of reactive bronchiolar or alveolar cells (in inflammation, status-post radiation, chemotherapy, etc.)
- Florid squamous metaplasia
- Florid bronchiolar metaplasia
- Crush artifact
- Strips of bronchiolar mucosa/mesothelial cells in TBBx’s
- Sarcoma with epithelioid features
- Metastatic carcinomas (many sites)

*AFIP Lung Tumor Fascicle, 3rd Series, Fascicle 13
What is going on here?

Groups of reactive type 2 cells in acute lung injury

Be wary of diagnosing adenocarcinoma in lung cytologies from pts with acute pneumonia, ARDS, etc.

Reactive squamous cells in the Bx

Squamous metaplasia by an infarct

TBBx: Carcinoma or not?

Sometimes reactive type 2 cells look like they are in submucosal lymphatics in TBBx's

No!
Sometimes reactive type 2 cells look like they are in submucosal lymphatics in TBBx’s

TBBx: Carcinoma or not? (from 1995 AFIP Lung Fascicle)

TBBx called adenoca- patient alive 1 yr later; clinically had a diffuse interstitial pneumonia

Peribronchiolar Metaplasia mimicks BAC

Squamous metaplasia in DAD can mistaken for Sq Ca

Imagine this in a small biopsy

The comfort of cilia

Again- Be wary of a lung cancer Dx in the setting of acute diffuse lung disease
Organizing DAD with squamous metaplasia

Frozen Section

Imagine this in a small biopsy

Small cell carcinoma overdiagnosis?

Atypical carcinoid

Small cell carcinoma vs. carcinoid/atypical carcinoid
The value of Ki-67 (proliferation marker) staining

Typical carcinoid
Small cell ca

Ki-67 Staining

3. MISDIAGNOSIS OF LUNG CANCER

Misclassification
- Small cell vs. nonsmall cell
- Subclassification of nonsmall cell
- Small cell vs. basaloide carcinoma
- IPOX criteria must be kept in perspective

Other misdiagnoses
- Sarcomatoid carcinoma as sarcoma
- Metastatic carcinoma as primary carcinoma and visa versa
- Synovial sarcoma as other sarcoma
- Many others
Small Cell vs. Nonsmall Cell Ca

Most small cell carcinomas don’t present a problem in diagnosis
>90% concordance among pathologists in older studies
(JCO 1990; 8: 402)

The number of problem cases is greatly magnified by selection bias in a consultation practice

Inter-observer Agreement in pathologic classification of lung cancer

>1350 cases from 1979-80 and 1987 reviewed (Jpn J Cancer Res 91:1, 2000)

Kappas from .72 - .87 comparing 2 reviewers and with original diagnosis

Virtual slides review by 24 pathologists (JCO 27: 15s, 2009)
SC vs nonSC: kappa = .55

Small Cell vs Nonsmall Cell ??

Called Small Cell Ca

Called SC/LC
Small Cell vs Nonsmall Cell Ca

What I do:
1. Routine H&E or cytology preps (WHO criteria)
   - Levels
   - Often stop here
2. IPOX features (new H&E also)
   - Use if supportive
   - If indeterminate or at variance, go back to #1 and to #3
3. Share with colleagues (total=an odd number)
4. Accept intra- and inter-observer disagreement; don’t look back!
5. Remember combined SC/LC Ca
6. Give patient the benefit of the doubt

PROGNOSTIC VS PREDICTIVE MARKERS

Pathologists have for years assessed prognostic markers; we will now be asked to assess predictive markers.
Histology as a Predictive marker:

- The importance of subtyping cases formerly grouped only as nonsmall cell carcinoma!
- Pathologists are now being asked to subtype nonsmall cell lung carcinoma based on studies suggesting differential response to various treatment regimens

Individualized medicine is the name of the game!

Proposed Algorithm- 2011*
For cases of pd NSCLCa on small biopsies

<table>
<thead>
<tr>
<th></th>
<th>Adca</th>
<th>SQCa</th>
<th>SQCa (if CK5/6-)</th>
<th>NSCLCa NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF-1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Napsin</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p63</td>
<td>+/-</td>
<td>+</td>
<td>diffuse+</td>
<td>-</td>
</tr>
<tr>
<td>CK5/6</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

< 25% called NSCLCa NOS with this algorithm


Primary lung cancer

1. RULE OUT SCLC
2. NSCLC

Immunohistochemical panel
TTF-1, p63, CK7, HMWCKs

ADC
TTF-1 +, p63 -, CK7 +, HMWCKs -

SQC
p63 +, TTF-1 –

Large cell carcinoma
P63 & HMWCKs negative

~2008
Slide courtesy G Rossi MD

Squamous Carcinoma

CK 5/6
p63
### Adenocarcinoma

TTF-1

### Squamous Carcinoma of the Lung

*(Current WHO criteria are clear: keratin and/or intercellular bridges)*

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Squamous Ca</th>
<th>Adenocarcina</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK 5/6</td>
<td>98%</td>
<td>11%</td>
</tr>
<tr>
<td>p63</td>
<td>97%</td>
<td>31%</td>
</tr>
<tr>
<td>TTF-1</td>
<td>7%</td>
<td>76%</td>
</tr>
</tbody>
</table>

*Data from Path/QImmunoQuery

*None are perfect*

### Recommendations for Nonsmall Cell Lung Ca Classification

**Use standard histologic criteria:**

- Squamous Ca: keratin, intercellular bridges
- Adenocarcinoma: glands, lepidic pattern, mucin, papillae, etc.
- Large cell Ca: Lack of above; indeterminate immunos
- Small cell Ca: LM criteria

**Immunohistochemistry** if above equivocal and for LCCa

**Report all your observations**

### IASLC/ATS/ERS

**International Multidisciplinary Classification of Lung Adenocarcinoma**

*(Travis WD; Brambilla E; Noguchi M; Nicholson AG; Geisinger KR; et al.)*

**Implications and recommendations for lung cancer diagnosis in small biopsy specimens**

*(J Thorac Oncol 2011;6:244 – 285)*
IASLC/ATS/ERS Classification (Resection Specimens)

Preinvasive Lesions
- Atypical adenomatous hyperplasia (AAH)
- Adenocarcinoma in situ (< 3 cm, former BAC)

Minimally Invasive
- < 3 cm lepidic predominant < 5 mm invasion
  - Non mucinous, muc, mixed

Invasive
- Lepidic predominant (former nonmuc BAC, with ≥ 5 mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin

Diagnostic Categories on Small Biopsies/Cytology Specimens

- Describe morphologic adenocarcinoma patterns present: e.g. acinar, lepidic, colloid
- If pure lepidic tumor state invasion cannot be excluded
Pathology Recommendation #9
On small biopsies and cytology specimens, subclassification is recommended whenever possible e.g. squamous, adca

Diagnostic categories when H&E features of differentiation are absent:
- NSCLC favor Adca (+ and – markers all favor)
- NSCLC favor Sqca (+ and – markers all favor)
PRIMARY LUNG CARCINOMA VS. METASTATIC CARCINOMA

Principles

Know the history
Know the clinical/radiologic pattern
Compare the histologies
Use immunoperoxidase discriminators (no lab has every antibody)
Molecular discriminators (usually not practical)

CASE HISTORY:

A 70-year-old woman with a history of breast carcinoma was found to have a coin lesion. This was wedged out (negative staple line margin) and sent for FS

Dx: Typical carcinoid tumor

Never underestimate pretest bias!

OTHER TRAPS

Metastatic breast ca mimics small cell ca
Usually soluble with Ipox

ER
TBBx
**OBJECTIVES**

**Know the areas of difficulty**
- Bland cells/mucinous cells
- Obscuring inflammation
- Metaplasias of various kinds
- Reactive type 2 cells
- Crush/other artifacts

**OBJECTIVES**

**Describe a strategy for dealing with them**
- Well fixed and prepared specimens
- Levels/additional cytopreps
- Share with colleagues
- Judicious IPOX (incl. another H&E)
OBJECTIVES

Review the criteria for the diagnosis of the common forms of lung carcinoma

By H&E and Pap
IPOX criteria
Indeterminate cases

SUMMARY

Most common “errors”/issues in lung cancer pathologic diagnosis
- Underdiagnosis of subtle cancers
- Subclassification
- Overdiagnosis of reactive changes
- Misdiagnosis: metast. vs primary, carcinoma vs sarcoma, reactive vs lymphoma, et. Al.