PROBLEMS IN THE INTERPRETATION OF NEOPLASTIC LUNG BIOPSIES

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Pulmonary Biopsies: Issues

• Is the biopsy adequate?
• Type of biopsy
  – Transbronchial or open
• Is the disease inflammatory or neoplastic?
• If neoplastic, what is the tumor type?

Pulmonary Biopsies: Issues

• Minimal requirements for interpretation:
  – Demographic information
  – Clinical differential diagnosis
  – Previous history of any malignancies
  – Radiographic findings
Pulmonary Biopsies: Issues

• Optimal diagnosis is dependent on the nature of the biopsy sample:
  – Bronchial wall only
  – Bronchial wall + alveolated parenchyma
  – Neither (e.g., soft tissue; pleura only)

Pulmonary Biopsies: Issues

• If the interpretation is non-neoplastic and no mass lesion is present in the specimen, but a radiographic mass is reported clinically, another biopsy is clearly necessary

Problems Centering on the Possible Presence of Neuroendocrine Carcinoma, Especially Grade 3 Small-cell Type
Frozen Section—Carcinoma vs. Artifact?

Mediastinoscopic Biopsy—Small Cell Neuroendocrine Carcinoma

High or Low-Grade Neuroendocrine Carcinoma?
Grade 1 NEC (Carcinoid)

Low- vs. High-Grade Neuroendocrine Carcinoma

- **Low-Grade**
  - Clear-cut organoidicity
  - Absence of apoptosis
  - Limited if any mitotic activity or necrosis
  - “Salt & pepper” chromatin
  - Discernible chromatin
  - Rosettes

- **High-Grade**
  - Sheet-like growth or only vaguely organoid architecture
  - Abundant apoptosis
  - Numerous mitotic figures
  - Necrosis
  - Nuclear molding

Neuroendocrine, Non-Neuroendocrine, or Mixed?
Mixed Neuroendocrine/Non-neuroendocrine Carcinoma

- The presence of a high-grade neuroendocrine carcinoma component will usually drive the tumor biology.
- Exact details of management depend on the institution at this juncture.
- Surgery vs. non-surgical therapy depends on STAGE, not on whether there is a small-cell carcinoma component in the biopsy.

High-Grade Neuroendocrine Carcinoma vs. Non-Hodgkin Lymphoma in Small Lung Biopsies: Morphology

- Carcinoma
  - Smudge artifact
  - Generally cohesive
  - Nuclear molding
  - Rounded nuclear membranes & dispersed chromatin
  - Numerous mitoses

- Lymphoma
  - Smudge artifact
  - Generally dysesive
  - No nuclear molding
  - Nuclear irregularity with folded contours
  - Greater range of cell sizes than in carcinoma
  - Apoptosis but limited if any mitosis
Which Type of *Non*-Neuroendocrine Carcinoma?
Poorly-Differentiated Squamous vs. Adenocarcinoma: Morphology & Histochemistry

- **Adenocarcinoma**
  - Nucleoli regularly present
  - Cells tend to grow in cords or rounded nests
  - Intracytoplasmic vacuoles may be present
  - PAS-D stain is positive in roughly 50% of cases

- **Squamous Carcinoma**
  - Nucleoli variably present
  - Cells arranged in a vaguely organoid fashion with a tendency toward spindling
  - Focal keratinization may be seen
  - PAS-D stain negative

PAS-Diastase Positivity in AdenoCA of Lung

Immunohistologic Markers of Squamous & Glandular Differentiation in Lung Tumors
p63 in Squamous Carcinoma—Also seen in Adenosquamous Carcinoma

Keratin 7, TTF-1, and Napsin-A may be seen in EITHER Adenosquamous Carcinoma or Adenocarcinoma

Napsin-A in AdenoCA

Keratin 5/6 may be seen in EITHER Adenosquamous Ca or Squamous CA
Molecular Testing in Lung Carcinoma: Quo vadis?
Sanja Dacic, MD & Samuel A. Yousem, MD
Am J Clin Pathol 2010; 134: 7-9

“It is time to admit that mutational analysis of lung carcinomas should be the standard of care.”

Special Tumors with Obvious Glandular Differentiation

Pseudopneumonic Non-Invasive Adenocarcinoma (NIA- Formerly Bronchioloalveolar Carcinoma): CT Scan
Non-Invasive Adenocarcinoma (NIA): Morphology

- Two types—mucinous and non-mucinous
- The non-mucinous type is more common
- Both show a “lepidic” growth pattern, with tumor cells mantling preexisting alveolar septa
- Cytologic features should be relatively bland, with common intranuclear invaginations of cytoplasm
- Significant intratumoral fibrosis precludes a diagnosis of true bronchioloalveolar carcinoma
Non-invasive Adenocarcinomas

NIA & AAAH: Different or Not?

- The morphologic, immunophenotypic, and genotypic characteristics of NIA/BAC and AAAH are identical, and the speaker regards them as part of the same continuum; AAAH is a “baby NIA/BAC”
- AAAH may be seen on chest radiographs, but is usually an incidental finding in lung resections done for other reasons; it measures up to 1 cm in diameter
- The principal value in recognizing AAAH is that it predicts potential multifocality, possibly in the contralateral lung as well
- When present at a resection margin, AAAH mandates increased surveillance for recurrent tumor

“Atypical Adenomatous Alveolar Hyperplasia” (“Baby-NIA”)
UNUSUAL PROBLEMATIC TUMORS OF THE LUNG
Primary Bronchopulmonary Melanoma

- Extremely rare; Virtually all melanomas in the lung are metastatic!
- The presence of in-situ melanoma in the bronchial epithelium is essential to even consider this diagnosis, because metastasis of mucocutaneous melanoma can be intrabronchial and solitary
- Confusion with anaplastic large-cell carcinoma or sarcomatoid carcinoma is possible
- Immunohistochemical reactivity for S100 protein, tyrosinase, melan-A, and HMB45 is expected in melanoma; keratin is virtually always absent
Mixed Tumor of the Lung (Pleomorphic Adenoma)

Salivary-Gland Analogue Tumors of the Lung

- Virtually all of the primary glandular neoplasms of the major salivary glands are recapitulated in the tracheobronchial tree
- Diagnostic criteria used in reference to the salivary gland also apply to pulmonary tumors
- Diagnostic traps principally center on confusion of such lesions with metastases, conventional adenocarcinomas of lung, and “carcinosarcomas” (metaplastic carcinomas)
Bronchial Oncocytoma

SPINDLE-CELL & PLEOMORPHIC NEOPLASMS OF THE LUNG
SARCOMATOID CARCINOMA OF THE LUNG: Synonyms

- Spindle cell carcinoma
- Carcinosarcoma
- Squamous cell carcinoma with pseudosarcomatous stroma
- Pleomorphic carcinoma
- Pseudosarcoma
- Pulmonary blastoma

SARCOMATOID CARCINOMA OF THE LUNG: Clinical Features

- Males predominate by a factor of 3:1; average age at diagnosis = 60 yrs.
- Usual history of heavy cigarette smoking
- Central lesions tend to smaller because of earlier discovery; they rather commonly have an endobronchial polypoid component
- Symptoms and signs are typically dependent upon tumor location, as true for other non-small-cell carcinomas of lung; recurrent pneumonia, wheezing, cough, & hemoptysis seen with central lesions; peripheral tumors are asymptomatic or may grow through pleura with production of chest pain
- “Pleurotropic“ peripheral SCL may yield symptoms & signs which imitate those of mesothelioma
SARCOMATOID CARCINOMAS OF THE LUNG: General Histologic Subtypes

• Monophasic SCL
• Homologous biphasic SCL
• Heterologous biphasic SCL

SARCOMATOID CARCINOMAS OF THE LUNG: Monophasic Tumors

• Rarest of SCL subtypes
• No light microscopic evidence of overt carcinomatous differentiation, despite extensive sampling
• Histologic image is identical to that of various sarcoma morphotypes, including fibrosarcoma, MHS, rhabdomyosarcoma, osteosarcoma, leiomyosarcoma, or chondrosarcoma
• Adjunctive studies are mandatory to make this diagnosis
• Extreme skeptics may question whether ALL reported examples of “heterologous” primary pulmonary sarcoma actually represent carcinomas, regardless of immunophenotypic or ultrastructural features
Monophasic Sarcomatoid Carcinoma of the Lung

SARCOMATOID CARCINOMAS OF THE LUNG: Heterologous Biphasic Tumors

• Formerly (and currently, by some) called “carcinosarcomas”
• Same general histologic characteristics as those of homologous SCL, except that “non-native” mesenchymal tumor patterns—such as osteosarcoma, chondrosarcoma, and rhabdomyosarcoma—are represented in the sarcomatoid component
• Analogous morphologically and conceptually to “heterologous” malignant mixed Mullerian tumor of the gynecologic tract (another form of biphasic sarcomatoid carcinoma)

Heterologous Differentiation in Sarcomatoid Carcinoma
**SARCOMATOID CARCINOMAS OF THE LUNG: Special Histologic Subtypes**

- Pulmonary “Blastoma”
- Pseudovascular (Angiosarcoma-like) SCL
- Inflammatory (Pseudotumor-like) SCL

**SARCOMATOID CARCINOMAS OF THE LUNG: Immunohistochemistry**

- Keratin “cocktails” label virtually all SCLs, but usually only with a multifocal, single-cell pattern; in biopsies, false-negativity may be seen because of sampling limitations
- Immunostains for EMA & collagen type IV or laminin are often positive as well; epithelial foci also may contain neuroendocrine markers
- Calretinin & podoplanin are typically absent in SCL
- Mesenchymal-like components are vimentin-reactive, & variably express actins, desmin, Myo-D1, myogenin, S100 protein, osteonectin, & CD56 or CD57, along with epithelial determinants in the same cell population
SARCOMATOID CARCINOMA OF THE LUNG: Differential Diagnosis

BIPHASIC TUMORS--
- Synovial sarcoma (primary or metastatic)
  - Metastatic MPNST
- Metastatic biphasic sarcomatoid carcinoma from kidney or other sites
- Mesothelioma (for pleural-based tumors)

MONOPHASIC TUMORS--
- Primary or metastatic monophasic synovial sarcoma
- True primary pulmonary sarcomas
- Metastatic sarcomas from other anatomic sites (uterus, deep soft tissue, etc.)
- Mesothelioma (for pleural-based tumors)
  - Metastatic melanoma
  - Inflammatory pseudotumors

Solitary Metastatic Melanoma in the Lung: A Mimic of Sarcomatoid Carcinoma

- Melanoma has the capacity to present with pulmonary metastasis in the absence of a known mucocutaneous tumor
- When it assumes a pleomorphic or sarcomatoid appearance, melanoma may simulate pulmonary sarcomatoid carcinoma or true sarcoma
- S100 protein and SOX10 are wise inclusions in immunohistologic evaluation of such tumors

Metastatic Melanoma with Sarcomatoid Features
“RHABDOID” CARCINOMA OF THE LUNG: A Special Variant of Pleomorphic Carcinoma

- Most examples of “extrarenal rhabdoid tumor” (ERT) are derived from some other form of “parent” neoplasm, and are therefore considered to be “composite” rhabdoid tumors
- Lung tumors exist with these characteristics, in which the rhabdoid component is variably prominent
- Their behavior is extremely aggressive, like that of ERT in general
  - Keratin is uniformly present

METASTATIC VS. PRIMARY CARCINOMAS IN THE LUNG
71 year old man with cough and wheezing, and an endoluminal lesion in the right mainstem bronchus.

Frozen Section

TTF-1 "RCC Antigen" (gp200) in Metastatic Renal Cell Carcinoma

“RCC Antigen” (gp200) in Metastatic Renal Cell Carcinoma

Right Renal Mass in Abdominal CT Scan
METASTATIC CARCINOMA IN THE LUNG

• Most often seen with carcinoma of breast or gastrointestinal tract; however, renal cell carcinoma is probably the most common somatic source of metastatic lung carcinoma with an “occult” primary lesion, and germ cell tumors also may behave similarly.
• Virtually any visceral carcinoma may involve the lungs secondarily.
• Stable solitary lesions are unusual as manifestations of metastatic disease.
• Several different types of metastatic carcinoma may involve the endobronchial lumen.

METASTATIC CARCINOMA IN THE LUNG

• Adenocarcinomas & germ cell tumors are much more amenable to determinations of their primary site than squamous carcinomas or neuroendocrine carcinomas.
• Ultrastructural and immunohistologic evaluations can be helpful in this regard, and more tumor-selective markers are being recognized yearly.

Prostate

Calm

Thyroid

Liver

Breast

Kidney

Prostate

Liver

Thyroid
SQUAMOUS OR NEUROENDOCRINE CARCINOMA IN THE LUNG-- PRIMARY OR SECONDARY?

• If a patient has had a previous squamous cell carcinoma (SCC) (e.g., in the head and neck) or neuroendocrine carcinoma (NEC), but it did not involve regional lymph nodes, a current SCC or NEC in the lung is much more likely to be a second primary tumor than a metastasis.

• Moreover, if a patient has 2 foci of intrapulmonary SCC or NEC, on the same side or contralaterally, the 2 tumors are probably synchronous primary neoplasms; pulmonary carcinomas only rarely metastasize back to the lung and virtually never in an isolated fashion.

CLINICOPATHOLOGIC CLUES SUPPORTING A PRIMARY NATURE FOR PULMONARY CARCINOMAS

• A “spiculated” configuration of the lesion on chest radiographs and CT scans.

• A fibroinflammatory reaction around the tumor and within it, especially if there is a central “scar.”

• Invasion by the tumor of arterial blood vessels or across the pleura into the thoracic soft tissue.