Current Concepts in the Pathological Diagnosis of Pulmonary Carcinomas

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Overview

• New WHO Classification
• Treatment update
• Staging issues

New WHO Classification

• Published in March 2015
• Incorporates terminology already widely used.
• Makes a few changes to large cell carcinoma reflected in other entities.
• Changes the name of sclerosing hemangioma.

Adenocarcinoma

• Based on 2011 IASLC/ATS/ERS classification.
• Eliminates the word “Predominant” from tumor type:
  • e.g. “Acinar predominant adenocarcinoma” is now just “Acinar adenocarcinoma”
  • HOWEVER...predominant is appended in diagnostic line (since most are heterogeneous)
Adenocarcinoma Types

- Lepidic
- Acinar
- Papillary
- Solid
- Micropapillary

- These are the major non-mucinous types
Cribriform pattern included in acinar

Papillary: Tumor cells grow on surface of fibrovascular cores

Solid: Sheets of tumor cells without gland formation
Solid without mucin production – former large cell

Micropapillary: Growth as small papillae without fibrovascular cores

Other Adenocarcinomas

- Invasive mucinous adenocarcinoma
- Colloid adenocarcinoma
- Fetal adenocarcinoma
- Cribriform pattern (currently under acinar, but behaves like solid)
Invasive mucinous adenocarcinoma: Often shows lepidic growth... admixed with acinar pattern.

Colloid adenocarcinoma: Abundant pools of mucin replacing alveoli... with tumor cells floating as clusters and alveolar walls.
Architecture as Grade

- Lepidic = Grade 1
- Acinar and Papillary = Grade 2
- Solid and Micropapillary = Grade 3
- Mucinous, colloid, fetal = Grade 3
- There is an additional grading scheme using nuclear grade and mitoses that helps divide the 2’s


Prognosis by Pattern

- Micropapillary type shows worse prognosis.

Any Micropapillary?

Central scar tissue (red), Acinar (yellow), Papillary (blue), and Micropapillary (green).


Semiquantitative Analysis

- Divide into patterns based on 5% increments. Then divide into predominant pattern.
- “Weak recommendation, low-quality evidence”

Adenocarcinoma Variants

- Does it matter to the clinician?
- What to put on the bottom line
  - Adenocarcinoma with a comment.
  - _____-predominant adenocarcinoma.
- I mention if micropapillary pattern is present.
- Lepidic pattern (AIS) has the same clinical intrigue as BAC used to have.
Spread through air spaces (STAS)

- Micropapillary clusters, solid nests, or single cells present within alveoli outside of the main tumor mass.
- Likely result in cases of localized recurrence after limited resections.
- Mention if present, particularly if present at margin (margin is negative for invasive tumor, but presence of STAS correlated with increased risk of local recurrence).

Judging Invasion

- Concept of AIS and MIA
- Clear invasion
  - pattern that is not lepidic
  - vascular or pleural invasion
  - STAS
  - fibromyxoid stroma (desmoplasia)

Judging Invasion

- Difficult to judge collapse of lepidic growth from acinar pattern
- Difficult to judge collapse of lepidic growth from papillary
- Some choose to just measure the region of collapse (Noguchi B type)
- Proper to measure the limited area of fibromyxoid tissue - difficult

Squamous Cell Carcinoma

- Previously defined histologically by keratinization
- Now two types:
  - Keratinizing
  - Non-keratinizing
Large Cell Carcinoma

- Previously used when no morphologic support for squamous cell or adenocarcinoma
- Now use immunohistochemical stains to help subclassify into:
  - Solid type adenocarcinoma
  - Non-keratinizing squamous cell carcinoma
  - Large cell carcinoma

Potential Pitfalls

- TTF-1:
  - Thyroid carcinoma
  - Entrapped pneumocytes
  - Gyn tumors (~80% ut. carcinosarcoma)
  - Neuroendocrine tumors
- Napsin-A:
  - Pulmonary macrophages (darker)
  - Renal cell carcinoma (~80%)
  - GI mucinous tumors (~80%)

Potential Pitfalls

- p63:
  - Entrapped basal layer
  - Urothelial tumors
  - Metastatic squamous tumors
  - Adenocarcinoma of lung
    - Require >10% of nuclei to stain
- p40:
  - More specific, but similar pitfalls

Mystery Case

- 64-year-old woman with right lower lobe lung nodule.
- CT-guided percutaneous fine needle aspiration performed.
Using the CT scan
Bone tumors, ILD, and now lung tumors

- Ground glass opacities versus solid masses
  - Determining extent of lepidic growth
  - Determining size of lesion
- Border of a lesion
  - Spiculated versus smooth
  - Typical adeno vs benign or fast-growing
- Multiplicity of lesions
  - Extrathoracic with met, lung met, synch primary
Sclerosing Pneumocytoma

- Formerly sclerosing hemangioma
  - “Sclerosing hemangioma (histiocytoma, xanthoma) of the lung”
- Characteristic radiologic appearance
  - Rounded edges are often either really bad (fast growing) or benign
- Characteristic immunoprofile
  - EMA positive, Keratin negative
  - TTF-1 positive, Napsin-A negative
- Immature pneumocytes with surface normal bronchiolar epithelium
Treatment Options

- Many tumors are typically treated with standard chemotherapy
- In recurrent and stage 4 tumors, and increasingly as first line, targeted treatments being used:
  - EGFR
  - EML4-ALK
  - ROS-1
  - BRAF
  - MET
  - MET
## Resistance Mutations
- EGFR TKI-treated tumors often develop additional mutations
  - commonly T790M within EGFR
  - Novel TKI
- Targeting other pathways being activated
  - MET, AXL

## Immunotherapy
- **PD-1 and PD-L1**
  - Programmed death 1 receptor and its ligands
  - PD-1 is an inhibitory checkpoint pathway in T cells
  - Some tumor cells have increased surface expression of PD-L1 (35-95% of NSCLC)
  - Currently in trials (although already FDA approved), most often for patients that have failed first and second line therapies

## Staging Issues
- Multiple nodules
- Pleural invasion
- Pleural drop metastases

## Multiple Nodules
- Sometimes difficult to determine if two tumor nodules represent
  - Synchronous primary tumors
  - Intraparenchymal metastases
**Martini-Melamed**

- Tumors are synchronous primaries if:
  1. Histologically different.
  2. Histologically similar but...
     - A. Arise from CIS
     - B. No tumor in shared lymphatics
     - C. No extrapulmonary mets

- At the time, histologically different meant SqC vs adeno, and CIS was Sq.CIS

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**Comprehensive Histologic Assessment**

- The “histologically different” component is expanded substantially
  - Percentage of adenocarcinoma subtype becomes significant
  - Cytologic features, stromal components also aid differentiation

- Additional concept of AIS/Lepidic growth
- To be discussed in the new AJCC – next year?

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**Pleural invasion**

- The many definitions of pleural invasion
  - What we want to think versus what there is data to support
  - Research from Japan (lots more EVG staining going on overseas)

- The prominent elastic layer (the visceral pleural elastica, aka the external elastic layer)
Pleural Invasion

• EVG for all tumors approaching the pleura.
• pT2a if external elastic layer is penetrated (visceral pleural elastica).
  – Raises stage from IA to IB in small tumors.
• Elastica of chest wall is variable, and it is sometimes difficult to assess chest wall invasion.
  – Look for penetration into parietal fat.
• Can use PL designations if desired
  – Past elastica PL1, on pleural surface PL2, into chest wall PL3

Pleural Drop Metastases

• Tumor studding on pleural surface
  • NOT direct extension (T2, PL2)
  • NOT subpleural lymphatic invasion with spread to other areas of the lung (T3 or T4)
• Similar prognosis as malignant pleural effusion (M1a)
Take Home Messages

- No significant changes to adenocarcinoma terminology since IASLC/ATS/ERS changes.
- Splitting of large cell using IHC.
- Sclerosing pneumocytoma.
- Targeted therapy, targeting resistance, immunotherapy.
- Not all multiple lesions mean poor prognosis.
- Treat the pleura with respect.