Case –based applications – part III

Los Angeles Society Of Pathologists
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CASE 1

- A 44-year-old woman with multiple lung nodules.
Tumor nodule 2
CASE 1

- TWO INDEPENDENT PRIMARY LUNG ADENOCARCINOMAS

- TUMOR NODULE 1
  - Invasive adenocarcinoma, acinar pattern dominant

- TUMOR NODULE 2
  - Invasive adenocarcinoma, lepidic pattern dominant
OUTLINE

- Clinical characteristics of multiple lung cancers
- Morphologic and molecular approach to staging and classification of multiple lung cancers
SYNCHRONOUS LUNG TUMORS

- 0.5-2% reported incidence

- Increased detection
  - HRCT
  - screening of smokers
  - closer follow up of patients after initial surgical resection
Clinical management of multiple lung tumor nodules

- Multiple nodules found on CT
  - PET/CT
  - Brain MRI
    - Extrathoracic Disease
    - Tissue Diagnosis Stage IV treatment
      - Positive
        - Same Lobe
          - Consider induction chemotherapy
          - Reevaluate for resection
        - Different Lobe/Contralateral Disease
          - Systemic Therapy for Stage IV Disease
      - Negative
    - No obvious Extrathoracic Disease
      - Mediastinoscopy
        - Ipsilateral Disease
          - Lobectomy vs. Sublobar resection based on pulmonary reserve, lesion site and location
          - Pathologic review for determination of SPLC
        - Contralateral Disease
          - Staged bilateral resections
          - Sublobar resection of smaller lesion
    - Exploration
PATHOLOGISTS ROLE

- Pathologist must identify tumors and describe them accurately (nodule number and size).

- Gross and microscopic location of the various tumors in relationship to each other needs to be described.

- Histologic evaluation.

- Statement to determine whether the tumors represent synchronous primaries or intrapulmonary metastases.
PROBLEM 1

- How to stage multiple synchronous lung carcinomas?
SYNCHRONOUS CARCINOMA STAGING

- **MULTIPLE PRIMARY LUNG CANCERS**
  - Different histology
  - Same histology
    - Anatomically separated
    - Temporally separated (2-4 years, no systemic metastases)

- **ADDITIONAL TUMOR NODULES (“SATELLITE NODULES”)**
  - Same histology
  - Same lobe
  - Grossly identified
  - No systemic metastases

7th AJCC TNM classification of synchronous lung tumors

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>AJCC 6th Edition</th>
<th>AJCC 7th Edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same lobe</td>
<td>T4</td>
<td>T3</td>
</tr>
<tr>
<td>Ipsilateral Different lobe</td>
<td>M1</td>
<td>T4</td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>M1</td>
<td>M1a</td>
</tr>
</tbody>
</table>
SYNCHRONOUS CARCINOMA STAGING

• When multiple tumors are of the same cell type, they should only be considered to be synchronous primary tumors if in the opinion of the pathologist, based on features such as associated carcinoma in situ or differences in morphology, immunohistochemistry, and or molecular studies, they represent differing subtypes of the same histopathological cell type, and…
PROBLEM 2

Are there any molecular tests that can improve staging of synchronous lung carcinomas?
Molecular approach to multiple lung tumors

- PCR clonality assays
  - DNA microsatellite analysis
  - X-chromosome inactivation analysis
- DNA mutational analysis
- Comprehensive aCGH, SNPs and gene expression analysis
DNA microsatellite analysis of synchronous adenocarcinomas of the lung

1\textsuperscript{st} tumor

2\textsuperscript{nd} tumor

HETEROGENOUS 30%
HOMOGENOUS 70%

Dacic S et al. AJSP 2005;29:897-902
Clonality analysis and p53 mutations

- Synchronous and metachronous tumors
- Adenocarcinomas and squamous cell carcinomas
- ~ 70% identical molecular profile

LIMITATIONS OF EARLY MOLECULAR STUDIES

- Relatively small number of analyzed cases
- Mixed analysis of synchronous and metachronous tumors
- Use of different methods and interpretation criteria
- Limited number of analyzed genes
Genomic profiling of multiple NSCLC

LIMITATIONS OF COMPREHENSIVE MOLECULAR STUDIES

- Relatively inadequate for clinical laboratories
- Significant cost
- Biostatistical support
- DNA quality may affect the analysis
- Performance status of different platforms may vary between laboratories
Can a routine molecular testing for oncogenic mutations be of any value in staging of synchronous lung carcinomas?
CAP/AMP/IASLC guideline for molecular testing of lung adenocarcinoma

1.5 : Expert Consensus: In patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested but testing of multiple different areas within a single tumor is not necessary.
CASE 5
Molecular results

Tumor nodule 1
Mutant EGFR
Exon 21 Sequencing
(T→G transversion)

Tumor nodule 2
EGFR WILD TYPE
PROBLEM 3

- Is there any role of IASLC/ATS/ERS classification in the staging of synchronous lung adenocarcinoma?
Two tumor nodules

TUMOR 1

TUMOR 2
PROBLEM 4

- How to stage multiple AIS, multiple MIA or AIS and MIA?
Synchronous primary tumors are most commonly encountered when dealing with either BAC or adenocarcinoma of mixed subtype with a BAC component
INTEGRATION OF CLINICAL, MOLECULAR AND HISTOLOGIC DATA

*Martini-Melamed*

Molecular assessment

Histology

Girard N. et al. AJSP 2009;33(12):1752
SUMMARY

- 7th AJCC staging of multiple lung cancers is suboptimal and multidisciplinary approach should be adopted

- Histologic assessment is important in staging of lung adenocarcinomas

- Molecular approach should be further investigated in prospective studies
CASE 2

69-year-old man with recurrent pleural effusions. Chest CT scan showed pleural thickening.
DIAGNOSIS

- Desmoplastic mesothelioma (DM)
OUTLINE

- Histological criteria for diagnosis of sarcomatoid/desmoplastic mesothelioma

- Ancillary studies in the diagnosis of sarcomatoid/desmoplastic mesothelioma
GENERAL RULES FOR DESMOPLASTIC MESOTHELIOMA

- Adequate tissue
  - large surgical specimens (core biopsies, pleural peel)
  - DM usually does not shed into the effusion fluid which may contain overlying reactive epithelioid mesothelial cells
- Talk to surgeons
- Review CT scans
- Ignore clinical history of asbestos exposure
- Do appropriate IHC
Differential diagnosis

- Fibrous pleurisy
- Sarcoma
**NOT** useful histologic criteria

- Cellularity
- Atypia (unless severe)
- Mitoses (unless atypical)
HISTOLOGIC CRITERIA

Storiform pattern

Desmoplastic mesothelioma

Often prominent
HISTOLOGIC CRITERIA
Necrosis

Fibrous pleurisy
Surface (if present)

Desmoplastic mesothelioma
Bland necrosis of collagenized tissue
HISTOLOGIC CRITERIA

Pleural thickness

Fibrous pleurisy
  Uniform

Desmoplastic mesothelioma
  Uneven, nodules
HISTOLOGIC CRITERIA

Zonation

Fibrous pleurisy
Hypercellular at the surface

Desmoplastic mesothelioma
Lack of zonation
HISTOLOGIC CRITERIA

Blood vessels

Fibrous pleurisy
Perpendicularly oriented

Desmoplastic mesothelioma
Paucity of blood vessels, no orientation
HISTOLOGIC CRITERIA

Stromal invasion

Fibrous pleurisy
Absent

Desmoplastic mesothelioma
Present
“FAKE FAT”

Husain et al. Arch Pathol Lab Med; 2012 Guidelines
S100, laminin, collagen IV

FAKE FAT

TRUE FAT
Immunohistochemical panels in sarcomatoid mesotheliomas

- Cytokeratins (AE1/3, Cam 5.2, CK7)
  - Focal, weak, variable
- Calretinin
  - Usually focal in <10% of cells
- D2-40

- Other mesothelioma markers and adenocarcinoma markers not helpful (WT-1, CK5/6, Ber-EP4, CEA, MOC31)
CYTOKERATIN IHC IN DM
Potential IHC markers in separation between benign and malignant mesothelial proliferations
IMMUNOHISTOCHEMISTRY

Reactive

Malignant

% positive cases

Attanoos RL. et al. Histopathology. 2003;43(3):231-8
GLUT-1

Reactive

Malignant

3%

67%

IMP3
*(insulin-like growth factor II messenger RNA-binding protein 3)*

Shi M. et al. AJSP 2011; 33(6): 878
Molecular markers in DM
GENETIC ALTERATIONS IN MALIGNANT MESOTHELIOMA

- Loss of p16 (9p21) is the most common genetic alteration in MM

- Homozygous deletion, point mutation, methylation
9p21 deletion and mesothelioma histology

- Epithelioid
- Biphasic
- Sarcomatoid
FISH FOR 9p21 (p16) DELETION

- Not deleted
- Deleted

Husain et al. Arch Pathol Lab Med ; 2012 Guidelines
SUMMARY

- Diagnosis of mesothelioma requires correlation between morphology, imaging studies and intraoperative findings.

- Interpretation of IHC in DM is challenging.

- No IHC markers are reliable in separation between benign and malignant mesothelial proliferations.

- FISH for p16 deletion is a promising diagnostic assay.
MAML2 translocation and prognosis

SUMMARY

- Diagnosis of lung tumors is mostly based on a routine H&E

- Limited specificity and sensitivity of molecular changes in lung carcinomas precludes development of molecular assays for diagnostic purposes

- Active research for markers for early detection of lung carcinomas, detection of lymph node metastases and molecular staging is in progress
CASE 3

• 54-year-old male with a history of stage I pancreatic carcinoma, status post Whipple resection and a solitary lung nodule.
Survival

![Survival Analysis Graph](image_url)
## Immunohistochemical staining patterns in tumors with mucinous features

<table>
<thead>
<tr>
<th></th>
<th>Pancreatic Metastases (% positive)</th>
<th>Lung Primaries (% positive)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK20</td>
<td>17/26 (65%)</td>
<td>5/18 (28%)</td>
<td>.03</td>
</tr>
<tr>
<td>CDX2</td>
<td>17/27 (63%)</td>
<td>1/18 (6%)</td>
<td>.0001</td>
</tr>
<tr>
<td>MUC2</td>
<td>4/24 (17%)</td>
<td>1/10 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>TTF-1</td>
<td>1/26 (4%)</td>
<td>16/21 (76%)</td>
<td>.0001</td>
</tr>
<tr>
<td>Napsin A</td>
<td>0/25 (0%)</td>
<td>3/9 (33%)</td>
<td>.014</td>
</tr>
<tr>
<td>SMAD4 loss</td>
<td>10/27 (37%)</td>
<td>8/28 (28%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
**KRAS MUTATIONS**

**TRANSVERSION MUTATIONS**
- substituting a pyrimidine for a purine, or purine for a pyrimidine

**TRANSITION MUTATIONS**
- substituting a purine for a purine, or a pyrimidine for a pyrimidine
## KRAS mutation type and smoking history

<table>
<thead>
<tr>
<th>MUTATIONS</th>
<th>NUCLEOTIDE</th>
<th>FORMER/CURRENT SMOKER</th>
<th>NEVER SMOKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12A</td>
<td>GGT → GCT</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>G12C</td>
<td>GGT → TGT</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>G12V</td>
<td>GGT → GTT</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>G13C</td>
<td>GGC → TGC</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>G13D</td>
<td>GGC → GAC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G12D</td>
<td>GGT → GAT</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>G12S</td>
<td>GGT → AGT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>-</td>
<td>90</td>
<td>12</td>
</tr>
</tbody>
</table>

Modified from
KRAS mutations in pancreatic carcinoma

- G12D
- G12V
- G12C
- G12R
- Other
## PANCREATIC VS. LUNG ADC

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td><strong>Mucious PDAC</strong></td>
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<tr>
<td>Mets</td>
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<tr>
<td>KRAS mutation</td>
<td>80%</td>
<td>54%</td>
<td>53%</td>
<td>81%</td>
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<tr>
<td>CK20 +</td>
<td>65%</td>
<td>72%</td>
<td>77%</td>
<td>59%</td>
</tr>
<tr>
<td>CDX2 +</td>
<td>63%</td>
<td>94%</td>
<td>94%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Mucinuous Lung</strong></td>
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<tr>
<td>PRimaryes</td>
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<tr>
<td>KRAS G12C</td>
<td>39%</td>
<td>95%</td>
<td>88%</td>
<td>62%</td>
</tr>
<tr>
<td>TTF-1 +</td>
<td>76%</td>
<td>96%</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>NapsinA +</td>
<td>33%</td>
<td>100%</td>
<td>100%</td>
<td>81%</td>
</tr>
<tr>
<td><strong>KRAS Mutated</strong></td>
<td></td>
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<tr>
<td>Lung Primaries</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>KRAS G12C</td>
<td>44%</td>
<td>96%</td>
<td>96%</td>
<td>41%</td>
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<tr>
<td>KRAS Mutated PDAC</td>
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</tr>
<tr>
<td>KRAS G12R</td>
<td>15%</td>
<td>99%</td>
<td>86%</td>
<td>74%</td>
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