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Beasley MB. The pathologist’s approach to acute lung injury. Arch Pathology Lab Med 2010;134: 719-727

Guinnee DG. Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities. Arch Pathology Lab Med 2010;134:691-701

Case Reports

I. Articles for Discussion

**Purpose:** To evaluate the differential expression of a panel of immunohistochemical markers in primary lung and metastatic breast cancer.

**Methods:** Immunohistochemical staining for TTF-1, Napsin A, surfactant apoprotein A, estrogen receptor, GATA-3, mammaglobin, and GCDFP-15 was evaluated on 197 lung carcinomas (158 adenocarcinomas, 39 squamous) and 115 invasive breast carcinomas (91 ductal, 24 lobular).

**Results:** All pulmonary squamous cell carcinomas were negative for all markers studied (Table 1). In lung adenocarcinomas, the percentage of positively staining cases was as follows: TTF-1 80%, Napsin 77%, surfactant apoprotein A 45%, GCDFP-15 2.5%, and ER 0.6%. All breast carcinomas were negative for TTF-1, Napsin A, and surfactant apoprotein A. The overall percentage of breast carcinomas (combined ductal and lobular) staining positively for the other markers studied is as follows: ER 74%, GATA-3 72%, mammaglobin 64%, and GCDFP-15 62%.

Overall, 84% of lung adenocarcinomas expressed either TTF-1 or Napsin, or both. The majority of lung adenocarcinomas negative for both markers were of solid type. The lone case of ER-positive lung adenocarcinoma showed only focal staining. Only focal staining was also observed in the four lung adenocarcinomas positive for GCDFP-15, two of which also staining for TTF-1 and/or Napsin A.

For breast carcinomas, 79% overall expressed at least one of the following: ER, GATA-3, or mammaglobin. Tumors negative for all 3 markers were all moderate to poorly differentiated ductal carcinomas.

**Table 1 Immunohistochemistry results**

<table>
<thead>
<tr>
<th>Lung adenocarcinoma</th>
<th>Lung squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>TTF-1</td>
<td>31</td>
</tr>
<tr>
<td>Napsin A</td>
<td>36</td>
</tr>
<tr>
<td>SFT-A</td>
<td>97</td>
</tr>
<tr>
<td>ER</td>
<td>157</td>
</tr>
<tr>
<td>GATA-3</td>
<td>158</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>158</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>154</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breast invasive ductal carcinoma</th>
<th>Breast invasive lobular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TTF-1</td>
<td>91</td>
</tr>
<tr>
<td>Napsin A</td>
<td>91</td>
</tr>
<tr>
<td>SFT-A</td>
<td>91</td>
</tr>
<tr>
<td>ER</td>
<td>30</td>
</tr>
<tr>
<td>GATA-3</td>
<td>32</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>41</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>43</td>
</tr>
</tbody>
</table>

**Discussion:** According to this study, ER expression that is more than focal is indicative of breast carcinoma. GCDFP-15 should be interpreted with caution when attempting to distinguish lung
adenocarcinoma from breast carcinoma due to its occasional expression in the lung adenocarcinoma. The combination ER or GATA-3/mammaglobin, will detect the majority (83%) of breast carcinomas and effectively exclude lung adenocarcinoma. The combination of TTF-1/Napsin A will detect a similar percentage of lung adenocarcinomas (84%) while excluding breast carcinoma.

**Take Home Message:** A four marker panel that includes ER or GATA-3, mammaglobin, TTF-1, and Napsin A appears adequate for distinguishing lung adenocarcinoma from breast carcinoma.


**Purpose:** To better characterize the clinical and pathologic features of granulomatous *P. jirovecii* pneumonia.

**Methods:** A retrospective review of 20 cases of pulmonary granulomatous Pneumocystis infection from 1988 to 2009 was undertaken. GMS stains were available and were positive for organisms morphologically consistent with Pneumocystis (Table 1) in all cases.

<table>
<thead>
<tr>
<th>TABLE 1. Diagnostic Features of Pneumocystis jirovecii and Histoplasma capsulatum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumocystis jirovecii</strong></td>
</tr>
<tr>
<td>Thin-walled cysts</td>
</tr>
<tr>
<td>2 to 5 μ</td>
</tr>
<tr>
<td>Collapsed forms common</td>
</tr>
<tr>
<td>Typically spherical</td>
</tr>
<tr>
<td>Nodulation</td>
</tr>
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</table>

**Results:** There were 15 males and 5 females. The most common presenting symptoms were dyspnea, cough, and fever; 2 were asymptomatic. The most common underlying medical conditions were HIV/AIDS (35%) and hematopoietic malignancies (30%). Imaging showed nodular infiltrates (50%), diffuse infiltrates (31%), or solitary nodules (19%). A definitive diagnosis was established by open lung biopsy (65%), autopsy (25%), or transbronchial biopsy (10%). Transbronchial biopsy was nondiagnostic in 7% of cases, BAL in 14%, FNA in 14%, and bronchial wash/brush in 65%. Forty-six percent of patients resolved and an equal percentage died of disease.

The pathologic findings are presented in Table 3.
Discussion: This is the largest series to date examining a granulomatous response to Pneumocystis in the lungs, which occurs most commonly in males with HIV/AIDS or malignancies. Due to the morphologic overlap between Pneumocystis and Histoplasma, careful attention should be paid to the distinguishing features of Pneumocystis, which include the absence of budding forms, spherical rather than oval shape, and larger capsular dots than Histoplasma.

Take Home Message: The diagnosis of Pneumocystic pneumonia may be overlooked when granulomas are present, as classic radiologic and pathologic findings are typically absent. Traditionally diagnostic procedures, such as BAL, are likely to be nondiagnostic in cases of granulomatous Pneumocystis pneumonia and prompt open lung biopsy should be considered.


Purpose: To evaluate whether PAX8 and h-caldesmon can successfully distinguish malignant mesothelioma from serous ovarian tumors.

Methods: Immunostaining for PAX8 and h-caldesmon was performed on archival tissue from 254 ovarian serous tumors (152 high-grade serous carcinomas, 10 low-grade serous carcinomas, 92 serous borderline tumors) and 50 mesothelial tumors (23 peritoneal malignant epithelioid mesotheliomas, 2 peritoneal WDPM, 1 peritoneal multiloculated inclusion cyst, and 24 pleural malignant epithelioid mesotheliomas).
Results: PAX8 stained was seen in 100% of low-grade serous ovarian carcinomas and serous borderline tumors, with the majority exhibiting diffuse moderate to strong intensity staining (Table 1). Nearly all (99%) of high-grade serous ovarian carcinomas showed PAX8 immunoreactivity, with diffuse weak to moderate intensity staining in two-thirds of cases. All pleural malignant mesotheliomas were negative for PAX8, but 9% of peritoneal malignant mesotheliomas showed focal and/or weak staining. Two WDPM and 1 peritoneal multiloculated inclusion cyst exhibited some staining. With the exception of 1 pleural malignant mesothelioma, all tumors were negative for h-caldesmon.

Discussion: PAX8 is highly sensitive (99.6%) and specific (95.7%) for ovarian serous neoplasms when compared with malignant mesothelioma. The h-caldesmon staining results presented in this study are discordant with those observed previously, calling into question the utility of h-caldesmon as a useful marker for mesothelioma.

Take Home Message: Diffuse intense PAX8 staining appears to be highly specific for ovarian serous tumors when compared with malignant mesothelioma. Although the authors of this study suggest this marker may be most useful in evaluating small biopsies, it is important to note that the specificity is not 100% and that rare cases of peritoneal malignant mesothelioma can be weakly and/or focally PAX8-positive.

<p>| TABLE 1. PAX8 and h-Caldesmon Staining in Ovarian Serous Tumors and Mesothelial Neoplasms |
|-----------------------------------------------|------------------|--------|--------|--------|------------|------------------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># POS/TOTAL (%)</th>
<th>4+</th>
<th>3+</th>
<th>2+</th>
<th>1+</th>
<th>h-Caldesmon</th>
<th># POS/TOTAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT</td>
<td>92/92 (100)</td>
<td>79</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0/92 (0)</td>
<td></td>
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<tr>
<td>LGSCA</td>
<td>10/10 (100)</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0/10 (0)</td>
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<tr>
<td>HGSCA</td>
<td>151/152 (99)</td>
<td>100</td>
<td>50</td>
<td>0</td>
<td>1</td>
<td>0/153 (0)</td>
<td></td>
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<tr>
<td>PLMM</td>
<td>0/24 (0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/24 (4)</td>
<td></td>
</tr>
<tr>
<td>PMM</td>
<td>2/23 (9)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0/23 (0)</td>
<td></td>
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<tr>
<td>WDPM</td>
<td>2/2 (100)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0/2 (0)</td>
<td></td>
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<tr>
<td>MLCM</td>
<td>1/1 (100)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/2 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion: PAX8 is highly sensitive (99.6%) and specific (95.7%) for ovarian serous neoplasms when compared with malignant mesothelioma. The h-caldesmon staining results presented in this study are discordant with those observed previously, calling into question the utility of h-caldesmon as a useful marker for mesothelioma. Take Home Message: Diffuse intense PAX8 staining appears to be highly specific for ovarian serous tumors when compared with malignant mesothelioma. Although the authors of this study suggest this marker may be most useful in evaluating small biopsies, it is important to note that the specificity is not 100% and that rare cases of peritoneal malignant mesothelioma can be weakly and/or focally PAX8-positive.


Purpose: To develop a multidisciplinary subclassification of lung adenocarcinoma.

Recommendations: The term BAC is to no longer be used. There will be a new category of minimally invasive adenocarcinoma (MIA). The category of mixed subtype adenocarcinoma will be dropped and tumors are to be categorized based on their predominant pattern with specification of the percentages of non-dominant patterns. Mucinous BAC will be reclassified as mucinous adenocarcinoma with lepidic pattern. In small biopsies of non-small cell carcinoma, a panel of special stains (mucin, TTF-1, CK5/6, p63) is recommended to distinguish between squamous cell, large cell, and adenocarcinoma.

Discussion: It will be interesting to see the recommendations presented in more detail in a full-length publication, but from what can be surmised, it looks like there will not be an
adenocarcinoma in situ category, hopefully making it easier to handle tumors with a lepidic
growth pattern that show focal sclerosis/stromal collapse. It is encouraging that the proposed
classification incorporates our understanding of molecular pathways of carcinogenesis by
recognizing mucinous adenocarcinoma with lepidic pattern as a separate category. BAC may
you rest in peace!

II. Articles for Notation

Original Articles

Carlini MJ et al. Mast cell phenotypes and microvessels in non-small cell lung cancer and
its prognostic significance. Hum Pathol 2010;41:697-705

Purpose: To assess the pathologic role and prognostic significance of mast cells in NSCLC.

Methods: Intratumoral and peritumoral mast cells were quantified immunohistochemically
using antibodies for tryptase and chymase in 65 NSCLC specimens. The density of microvessels
was also quantified using CD34.

Results: There was a positive correlation between intratumoral mast cell and microvessel
densities. Low mast cell density was associated with worse 5-year survival in a subset of stage I
patients.

Take Home Message: The correlation between mast cell and microvessel densities supports the
concept that mast cells are involved in the angiogenic process. The association between worse
prognosis and low mast cell density suggests mast cells exert an antitumor effect in NSCLC.

Chen Z et al. Expression of nestin in lymph node metastasis and lymphangiogenesis in non-
small cell lung cancer patients. Hum Pathol 2010;41:737-744

Purpose: To assess expression of the stem cell marker nestin in NSCLC and correlate its
expression with clinicopathologic characteristics.

Methods: Nestin expression was evaluated in 52 NSCLC specimens by immunohistochemistry
and correlated with clinicopathologic characteristics.

Results: High nestin expression, which was observed in 51.9% of cases, correlated significantly
with poor differentiation, adenocarcinoma histology, N2 lymph node metastasis, and lymphatic
vessel density.

Take Home Message: Nestin appears to play a critical role in tumor-induced lymphangiogenesis
and nodal metastasis in NSCLC.

Purpose: To assess immunohistochemical expression of metastasis-associated protein CD24 in NSCLC and determine its prognostic significance.

Methods: CD24 expression was evaluated in a tissue microarray of 267 consecutive cases of NSCLC by immunohistochemistry and correlated with clinicopathologic parameters.

Results: High CD24 expression (>10% positive cells) was associated with adenocarcinoma histology (38% vs. 23% in squamous cell; p = 0.023) and with a significantly higher risk of disease progression and cancer-related death.

Take Home Message: CD24 appears to be a useful biomarker in NSCLC, indicative of aggressive tumor behavior.

Review Articles

Allen TC. Pathology of small airways disease. Arch Pathology Lab Med 2010;134: 702-718

A very thorough review that even includes a discussion of airway damage induced by ingestion of S androgynus, a common vegetable in Malaysia!

Beasley MB. The pathologist’s approach to acute lung injury. Arch Pathology Lab Med 2010;134: 719-727

Another excellent review that discusses not only diffuse alveolar damage, but also acute fibrinous and organizing pneumonia, eosinophilic pneumonia, and diffuse alveolar hemorrhage with capillaritis.

Guinnee DG. Update on nonneoplastic pulmonary lymphoproliferative disorders and related entities. Arch Pathology Lab Med 2010;134:691-701

A nice overview that explores current concepts with respect to follicular bronchiolitis, lymphocytic interstitial pneumonitis, and nodular lymphoid hyperplasia, as well as IgG4-realted sclerosing disease.


This practical “how-to” has enough pearls (e.g., when you see neutrophils in granulomas, think Blastomyces) that even the experts among us might find it worthwhile reading.
Case Reports


Case Summary: A 50-year-old woman who had undergone radiofrequency pulmonary vein ablation to treat atrial fibrillation presented acutely with cough, hemoptysis, and pleuritic pain. She was found to have pulmonary venous occlusion and lobar infarction with accompanying pulmonary hypertensive changes in the resected lobe.

Take Home Message: Radiofrequency ablation of arrhythmogenic foci in the pulmonary veins is an effective treatment of atrial fibrillation, but carries about a 2% risk of subsequent pulmonary vein occlusion. A variety of pathologic pulmonary findings have been described, including venous infarcts, with their distinct septal distribution, and chronic venous hypertensive changes. Consider this rare cause when you encounter pulmonary venous hypertensive changes similar to those seen with mitral stenosis and sclerosing mediastinitis.