# PULMONARY PATHOLOGY JOURNAL CLUB
(October 2009 articles)
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Butnor et al. Protocol for the examination of specimens from patients with primary non-small cell carcinoma, small cell carcinoma, or carcinoid tumor of the lung. Arch Pathol Lab Med 2009;133;1552-1559


Chua A-P et al. Trees don't grow in the lungs! Chest 2009;136:1187
I. Articles for Discussion


Purpose: To identify consistent pulmonary histologic features in patients with known autoimmune pancreatitis and understand more about patients with similar histologic features in whom the presence or absence of autoimmune pancreatitis is unknown, as well as elucidate levels of IgG4+ cells in various lung diseases.

Methods: Six lung biopsies from autoimmune pancreatitis were studied along with 12 other cases with similar histologic features and compared staining for IgG4 to various other lung diseases.

Results: In patients with autoimmune pancreatitis, consistent histologic findings included increased levels of IgG4, pulmonary vessel endothelialitis, active fibrosis, plasma cell and histiocyte-rich lymphangitic inflammatory infiltrates, fibrinous pleuritis, and prominent lymphatic dilatation with emperipolesing histiocytes. Increased IgG4 levels were also seen in Rosai-Dorfman disease and in some IMTs.
Take Home Message: The pulmonary histologic features in patients with increased IgG4 cells and autoimmune pancreatitis is distinctive. The significance of the overlap between the high levels of IgG4 and some of the histologic features in such patients and patients with Rosai-Dorfman disease requires further study.

Purpose: To report the clinical and histologic findings in 5 patients who developed biopsy-proven interstitial pneumonitis associated with preleukemic myeloid neoplasia.

Methods/ Results: The 5 patients included 3 females and 2 males with a mean age of 49 years. CT scanning disclosed diffuse bilateral ground glass upper lung zone-predominant opacities. At the time of lung biopsy, 3 patients had a small percentage of circulating blasts. All cases showed lymphoid infiltrates with a DIP-like reaction. Although small numbers of MPO-positive interstitial myeloid cells were seen, the quantity was insufficient for a diagnosis of myeloid sarcoma.

Take Home Message: Upper lung zone-predominant diffuse cellular and fibrosing interstitial pneumonitis with a DIP-like reaction may be a distinctive pulmonary interstitial disease related to myeloid neoplasia. However, the relevance of this observation will require a larger number of cases. A hypersensitivity response cannot be excluded, as 2 of the 5 patients in this study received cytotoxic therapy prior to the development of pulmonary disease.

**Purpose:** To explore the origins of fibroblasts in bleomycin-induced lung fibrosis through *in vitro* and mouse studies.

**Methods/ Results:** Bone marrow chimera mice with given intratracheal bleomycin and cultured type 2 cells were examined using immunohistochemistry. Lung epithelium-derived fibroblasts, through a process of epithelial-mesenchymal transition, in combination with bone marrow progenitors, accounted for just over one-half of lung fibroblasts 2 weeks after injury.

**Take Home Message:** Although epithelial-mesenchymal transition, an interesting and not well understood phenomenon, as well as bone marrow progenitors, contribute to post-bleomycin lung fibroblasts, the origin of the remainder of fibroblasts that can be detected in this setting remains to be elucidated.


**Case Summary:** The authors report the first case of angiomatoid fibrous histiocytoma (AFH) to apparently arise in the lung in a 46-year-old male with a one-month history of chest tightness. CT scanning showed a well-demarcated homogenous parenchymal mass. Histologically, the resected tumor was composed of multiple nodules of EMA and focally desmin, CD68, and CD163-positive histiocytoid cells in a vaguely storiform to whorled pattern surrounded by a fibrous pseudocapsule and peritumoral lymphoplasmacytic inflammation (see photomicrograph). Focal myxoid change was seen. The tumor showed EWS/ATF1 gene fusion by PCR. The patient was free of disease 1 year post-resection.
Take Home Message: While typically occurring in the deep dermis and subcutis of children and young adults, this case illustrates that AFH can occur in middle-age patients in unusual sites. The morphologic features of AFH are rather non-descript, leading to frequent misdiagnosis as other tumors such as meningioma, IMT, and follicular dendritic cell sarcoma. A helpful clue to the diagnosis of AFH is the peritumoral shell of lymphoplasmacytic inflammation.

II. Articles for Notation

Original Articles


Purpose: To describe a cohort of patients who presented with interstitial lung disease (ILD) of unclear etiology who underwent minor salivary gland biopsy to confirm a diagnosis of Sjogren syndrome (SS).

Methods: Thirty-eight patients with ILD of unknown etiology underwent minor salivary gland biopsy based on the recommendation of rheumatologic consultation.

Results: Of the 38 patients, 34% had a positive salivary gland biopsy for SS, 77% of which had sicca symptoms. However, 23% of those with a positive biopsy were negative for ANA, RF, and SS-A and B autoantibodies.

Take Home Message: While the authors conclude that salivary gland biopsy allowed for a more precise classification in this cohort, they state that the identification of underlying SS did not affect the management of ILD in these patients, leaving one to wonder about the significance of this observational study.


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**TABLE 2. Main Differential Diagnoses of Pulmonary Spindle Cell Tumors**

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<th>Morphology</th>
<th>Immunophenotypic Features</th>
<th>Genetics</th>
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<tr>
<td>AFH</td>
<td>Peritumoral lymphoplasmacytic infiltrate; multinodular growth pattern; dendritic cell tumor-like morphology</td>
<td>Frequently positive for desmin, CD68, EMA, and CD99. Positive for actin, and variably cytokeratin, ALK.</td>
<td>EWS/CREB1, EWS/ATF1, or FUS/ATF1 gene fusion, ALK gene translocation</td>
</tr>
<tr>
<td>IMT</td>
<td>Inflammatory component intimately intermingled with neoplastic spindle cells; neoplastic cells with distinct cell borders, amphophilic cytoplasm, and vascular nuclei</td>
<td>Positive for EMA, negative for desmin, CD68, and CD99.</td>
<td>Deletion of chromosome 22</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Tumor cells with indistinct cell borders arranged in whorls and sheets; rare cases may have heavy lymphoplasmacytic infiltrate, but not in the form of a shell</td>
<td></td>
<td></td>
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<tr>
<td>FDC sarcoma</td>
<td>Spindle to oval cells with indistinct cell borders arranged in fascicles, whorls, or vague nodules; infiltrated by small lymphocytes but few plasma cells; tumor cells have vesicular chromatin, distinct nucleoli, and delicate nuclear membrane</td>
<td>Positive for FDC markers (CD21, CD23, and CD35).</td>
<td>Unknown</td>
</tr>
<tr>
<td>Spindle cell</td>
<td>Cohesive nests and irregular fascicles of overtly malignant cells with hyperchromatic nuclei and distinct nucleoli; diagnostic if a component of conventional carcinoma is present</td>
<td>Positive for keratin and p63, and variably TTF-1</td>
<td>Variable</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
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Take Home Message: While the authors conclude that salivary gland biopsy allowed for a more precise classification in this cohort, they state that the identification of underlying SS did not affect the management of ILD in these patients, leaving one to wonder about the significance of this observational study.

Purpose: Although designated as an original article, this is essentially a case report describing lung cysts in a patient with Birt-Hogg-Dube (BHD). The distribution of the BHD gene-encoding protein folliculin in the lungs is also reported.

Methods: Immunohistochemistry for folliculin was performed on formalin-fixed paraffin-embedded tissue from the patient's resected lung tissue.

Results: BHD lung cysts were found to be lined by pneumocytes and located in the vicinity of the interlobular septa and visceral pleura. Protrusions of veins into some of the cysts were observed. No associated stromal proliferation or inflammatory cell infiltrate was seen. folliculin staining was detected in the pneumocytes lining the cysts and was also seen in bronchiolar epithelium, alveolar macrophages, and some type 2 pneumocytes away from the cysts in a distribution no different from that of normal control lungs.

Take Home Message: In contrast to blebs and some emphysematous bullae, BHD lung cysts appear to show no associated inflammatory and/or stromal proliferative reaction.


Purpose: To clarify the accuracy of pathologic diagnosis of mesothelioma in Japan.

Methods: Mesothelioma death cases were extracted from a retrospective review of “Vital Statistics of Japan” for 2003-2005 and available pathological materials were reviewed.

Results: Among 2742 mesothelioma death cases, pathological material was available for review in 382 cases. Following review, 17% of cases were categorized as “definitely not/unlikely” mesotheliomas and 71.5% were categorized as “probable/definite” mesotheliomas. The percentage of “probable/definite” mesothelioma was much higher in males (74.3% pleural and 87.5% peritoneal) than in females (59.2% pleural and 22.2% peritoneal).

Take Home Message: Not unexpectedly, the accuracy of a diagnosis of mesothelioma in females is relatively low, especially of tumors arising in the peritoneum.


Purpose: To clarify the role of the proinflammatory cytokine IL-32 in lung carcinogenesis.

Methods: Immunohistochemical expression of IL-32 was correlated with clinicopathologic and survival data in 23 premalignant (AAH, squamous metaplasia and dysplasia) lung lesions and 148 lung cancers.

Results: In contrast to squamous cell carcinoma and its precursors, in which IL-32 expression was lacking in 76%, 73% of adenocarcinomas, 64% of large cell carcinomas, and 77% of small
cell carcinomas showed expression. IL-32 expression was strongly correlated with lymph node metastases, particularly in tumors that also showed an IL-32-positive leukocyte infiltrate.

**Take Home Message:** IL-32 likely has a role in the pathogenesis of most lung cancers, but its impact on the development of squamous cell carcinoma is less certain. Given its association with lymph node metastases, IL-32 may be useful as a prognostic marker.


**Purpose:** To describe the frequency of KRAS amplification in non-small cell lung cancer (NSCLC).

**Methods:** FISH was used to assess the presence or absence of KRAS amplification in 100 consecutive NSCLCs.

**Results:** KRAS amplification was detected in 7 of 100 cases (3 adenocarcinomas, 2 squamous cell carcinomas, and 2 large cell carcinomas) with a concurrent activating KRAS mutation in 4. KRAS amplification was associated with increased p21 expression.

**Take Home Message:** In contrast to KRAS-mutated NSCLCs, which are strongly associated with cigarette smoking, poor prognosis, and resistance to tyrosine kinase inhibitors, little is known about the role of KRAS amplification in lung tumors. Although the authors report that a "sizeable subgroup" of NSCLCs (7%) harbor KRAS amplification, the clinical exploitability of this relatively low-frequency finding remains to be determined.

**Review Articles/Recent Advances/Special Features**

**Bertino E et al.** *Pulmonary neuroendocrine/carcinoid tumors: a review article. Cancer 2009;125:4434-4441*

A general review of the spectrum of pulmonary neuroendocrine tumors with a nice summary table of histologic criteria and information about current and investigational treatments.

**Butnor et al.** *Protocol for the examination of specimens from patients with primary non-small cell carcinoma, small cell carcinoma, or carcinoid tumor of the lung. Arch Pathol Lab Med 2009;133;1552-1559*

Details the pathological parameters important for staging lung cancer resection specimens according to the forthcoming 7th edition of AJCC.


A comprehensive review of clinical aspects of ANCA-associated vasculitides.

An exploration of how histology impacts on the clinical benefit of specific chemotherapeutic or targeted therapy regimens in non-small cell carcinoma. Includes a discussion of data showing which histologic types are most responsive to standard platinum-based chemotherapy and EGFR-based therapies.

Case Reports


Case Summary: A 45-year-old male presented with dyspnea of 2 weeks' duration and a bilateral ankle rash. He had a history of hepatitis C and was status post multi-modality treatment of embryonal testicular carcinoma metastatic to the lungs 18 months prior. CXR disclosed pneumothorax and multiple pulmonary nodules. He was found to be c-ANCA and PR3-positive. Skin and lung wedge biopsies both showed well-formed granulomas. Tissue cultures returned positive for *Mycobacterium avium* complex (MAC).

Take Home Message: ANCA positivity can, albeit rarely, be seen in patients with MAC pulmonary infection (as well as a host of other diseases, including rheumatoid arthritis, ulcerative colitis, Crohn disease, autoimmune hepatitis, sarcoidosis, and infection).


Case Summary: A 67-year-old women with a history of breast cancer presented with progressive dyspnea of 2 weeks duration and was found to have pulmonary hypertension. She rapidly developed respiratory failure and succumbed shortly after presentation. An autopsy disclosed pulmonary tumor emboli of metastatic breast carcinoma.

Take Home Message: The most common symptom of pulmonary tumor embolism is progressive dyspnea, seen in > 70% of cases. Survival in those diagnosed antemortem is brief (4-12 weeks). Breast carcinoma is the most common cause, followed by gastric and pulmonary primary tumors.


Case Summary: A 35-year-old female smoker presented with a 2-week history of rapidly progressive dyspnea on exertion. Chest imaging showed pneumothorax, bullae, and bilateral diffuse reticular infiltrates. Lung biopsy showed non-caseating granulomas and she was diagnosed with bullous sarcoidosis.
Take Home Message: Bullous sarcoidosis is more common in males. The mechanism of bulla formation is uncertain, but may be related to ball-valve obstruction with endobronchial lesions leading to peripheral air-trapping and/or result from retraction and collapse around diseased areas of lung. This form of sarcoidosis is likely under-recognized, as the findings are easily attributed to smoking-related COPD. Bullous sarcoidosis seems to respond poorly to corticosteroids and in some cases progresses rapidly to cor pulmonale.


Case Summary: A 27-year-old male of Puerto Rican ancestry presented with progressive dyspnea and decreased exercise tolerance. CT scanning disclosed diffuse ground glass opacities, traction bronchiectasis, and honeycombing. Careful additional questioning and examination disclosed oculocutaneous albinism and a bleeding diathesis. The patient was diagnosed with Hermansky-Pudlak Syndrome (HPS) and underwent lung transplantation. The resected native lung showed pulmonary fibrosis with unusually large vacuolated histiocytes and pneumocytes containing PAS-positive brown pigment.

Take Home Message: HPS is an autosomal recessive disorder most commonly found in persons from Puerto Rico characterized by defective lysosome-related organelles, including lamellar bodies in type 2 pneumocytes, resulting in deposition of ceroid. Degeneration of type 2 pneumocytes is thought to contribute to pulmonary fibrosis. Pulmonary fibrosis in HPS is characteristically uneven in distribution and lacks the subpleural accentuation and fibroblast foci seen in UIP.

Letters to the Editor

Chua A-P et al. Trees don't grow in the lungs! Chest 2009;136:1187

Spurred on by an apparent medical hoax in which a tree was said to be found in a Russian botanist undergoing resection of a “lung tumor,” the authors attempt to tackle the question of whether aspirated seeds can grow in the human lung.