PULMONARY PATHOLOGY JOURNAL CLUB
(November 2008 articles)
December 15, 2008

Articles for Discussion


Articles for Notation
Original Articles


Current Topics/ Review Articles


**Unusual Tumors/Cases**


**Research**


**Clinically related articles of interest**

I. Articles for Discussion


Purpose:
To assess the validity of the proposed International Association for the Study of Lung Cancer Staging 2009 scheduled revision. To discuss the utilities and drawbacks of the new staging system.

TABLE 1. Summary of the proposal for changes to the sixth edition of the TNM classification

<table>
<thead>
<tr>
<th>Tumor size</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Reclassify T2 tumors &gt;7 cm as T3</td>
<td></td>
</tr>
<tr>
<td>• Subclassify:</td>
<td></td>
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<tr>
<td>• T1 as</td>
<td></td>
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<tr>
<td></td>
<td>— T1a (≤2 cm) or</td>
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<tr>
<td>— T1b (&gt;2 cm to ≤3 cm); and</td>
<td></td>
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<tr>
<td>• T2 as</td>
<td></td>
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<tr>
<td>— T2a (&gt;3 to ≤5 cm or T2 by other factor and ≤5 cm) or</td>
<td></td>
</tr>
<tr>
<td>— T2b (&gt;5 to ≤7 cm)</td>
<td></td>
</tr>
<tr>
<td>Separate tumor nodule</td>
<td></td>
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<tr>
<td>• Reclassify T4 tumors with additional nodules in the lung (primary lobe) as T3</td>
<td></td>
</tr>
<tr>
<td>• Reclassify M1 with additional nodules in the ipsilateral lung (different lobe) as T4</td>
<td></td>
</tr>
<tr>
<td>• Subclassify M1 with additional nodules in the contralateral lung as M1a</td>
<td></td>
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<tr>
<td>M factor</td>
<td></td>
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<tr>
<td>• Reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) from T4 to M1a</td>
<td></td>
</tr>
<tr>
<td>• Subclassify M1 with distant metastases (outside the lungs or pleura) as M1b</td>
<td></td>
</tr>
<tr>
<td>Stage grouping</td>
<td></td>
</tr>
<tr>
<td>• Reclassify T2a N1 tumors (≤5 cm) as stage IIA (from IIB)</td>
<td></td>
</tr>
<tr>
<td>• Reclassify T2b N0 tumors (&gt;5–7 cm) as stage IIA (from IB)</td>
<td></td>
</tr>
<tr>
<td>• Reclassify T4 N0 and T4 N1 tumors as stage IIIA (from IIIB)</td>
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</table>
Methods:
Retrospective review of patients at Aichi Cancer Center and Hospital who had a surgical resection with nodal dissection for primary NSCLCs (n=1556). Data from each patient was recorded from the chart including adjuvant and induction therapies, date of last follow-up and death from any cause. All patients were followed for at least 5 years or until death. Survival statistics for these cases were reviewed based on the new staging system proposed by the IASLC.

Results:
The proportion of patients with stage IIA disease was markedly increased by reclassifying patients with stage IB and IIB disease. Survival analysis of the patients in the old staging system for stages IB and IIA were nearly identical; in the new system the survival curve showed a stepwise deterioration as the stage increased (except for stage IV disease). The 5 year survival rate of patients with satellite tumor nodules was 36% in the new staging system; 17% in the T4 group (old staging system). No prognostic difference was found between the new T1a and T1b classifications.

Take home message:
The authors support the proposals for the new TNM staging system of lung cancer based on the results of this study. Patients with stage III and IV were not adequately represented in this study because many of them are unresectable. The new proposal includes a zone concept for lymph nodes (there is currently confusion on which nodes are where depending on the map you use).


Purpose:
To assess the safety and efficacy of surveillance bronchoscopy (transbronchial biopsy and bronchoalveolar lavage) in lung transplant recipients.

Methods:
Review of all routine surveillance and clinically indicated bronchoscopy procedures (n=353, 232 were routine) performed from Oct 2000 to Oct 2001 in the Alfred Hospital in Melbourne, Australia. Demographic data was recorded. Any complications were recorded for each procedure, including sedation-related respiratory depression, bleeding, pneumothorax, fever. All transbronchial biopsies were reviewed by a pathologist and graded according to the ISHLT grading system; viral infection, PTLD, organizing pneumonia and malignancy were looked for.
Results:
The rates of “useful” diagnoses (those resulting in a therapeutic change) were similar for both SB (18.1%) and CB (13.2%).
31.4% of SBs at <3 months and 36.7% of SBs at 3-12 months had clinically significant results
Higher incidence of infection in CBs (33.1%) than SB (17.2%).
35.7% of all bronchoscopies had a clinically useful outcome that altered management
Silent acute rejection was most common up to 3 months post-tx.

Take home message:
Bronchoscopy with TBBX is safe in lung tx patients beyond the first year out
SB with BAL and TBBX in stable lung tx patients <1 year has a high utility for clinically silent acute rejection and infection
After 1 year tx, the diagnostic yield of bronchoscopy and BAL is high and outweighs the procedural risk (not so for TBBX)
Authors suggest SB with TBBX for at least 1 year post-tx, then SB with BAL at 18 months post-tx, then annually after 2 years.


Purpose:
A report of 3 cases of interstitial lung disease with lymphoplasmacytic vasculitis and abundant IgG4-positive plasma cells with review of the literature and pathologic features of IgG4-related lung disease.

Methods:
Reviewed were 3 cases of interstitial lung disease with dense lymphoplasmacytic vasculitis and infiltration from Kyoto University Hospital, Japan. Two of the cases were consultation cases.
Patient 1: 65 y/o male with nodular lesion in left lung, never smoked, labs normal, CT showed ill-defined 3.2cm spiculated mass in LLL hear hilum, PET positive, nodes NPD, LLL lobectomy. Serum IgG4 elevated, submandibular and parotid swelling.
Patient 2: 78 y/o with DOE. Non-smoker X30 years. CT – multifocal areas of ill-defined consolidations in subpleural bilateral lower lobes. Swollen mediastinal lymph nodes. LIP diagnosed initially. Developed mild sicca syndrome. ANA elevated (1:80). Lung lesion disappeared after 11months and prednisone therapy.
Patient 3: 74 y/o male DOE. Right sided pleural effusion on CXR. Vague nodular lesion in RUL and extensive pleural thickening on thoracoscopy.
Results:
Histology: Mononuclear cell infiltration along bronchovascular bundles and intralobular and alveolar septa. Vasculitis with subendothelial lymphoplasmacytic infiltration. >90% of plasma cells IgG positive. IgG4 positive plasma cells in 85%, 47% and 46% of the 3 cases. No monoclonal heavy chains genes or T-cell receptor gamma-chain genes were detected.

Take home message:
Differential diagnosis includes malignant lymphoma, lymphomatoid granulomatosis. LYG-G1 is the main ddx. Lack of atypical cells and presence of IgG-4 positive plasma cells favors IgG-4-related disease. IgG4-related lung disease characterized by nongranulomatous and nondestructive vasculitis. Small case report of only 3 cases.


Purpose:
Report of 4 patients with nodular amiodarone lung disease (ALD) with detailed analysis of histopathology to alert pulmonary pathologists of the histology of this entity so that it will be recognized more readily since the clinical history is often incomplete and without mention of the use of amiodarone.

Methods:
Case 1 – 68 y/o male, polyradiculoneuropathy, atrial fibrillation with pacemaker (on Coumadin and Amiodarone), chronic non-productive cough X3 months. Chest CT showed 2.6cm irregular mass in RUL and prominent interstitial markings bilaterally. PET positive. Underwent resection. Pathology revealed an abscess. Amiodarone stopped. Interstitial markings decreased and patient gradually improved.


Case 3 – 60 y/o male with two pulmonary masses, 3.5cm RLL, 2cm LUL. PET positive. Heavy smoker. Wedge resection performed. Unknown to pathologist, he was on Amiodarone which was stopped. CXR cleared and patient improved.


Pathology: Foci of basophilic necrosis with rim of eosinophilic necrosis or solid inflammation. Vacuolated histiocytes surrounded the necrosis. Neutrophils within the necrosis and involved bronchioles. Markedly vacuolated histiocytes in non-necrotic areas.

Results:
ALD looks like interstitial pneumonitis. Bronchiolitis obliterans, organizing pneumonia, pulmonary hemorrhage, DAD and nodular inflammation can be seen. Vacuolization of
cytoplasm in pneumocytes, endothelial cells and histiocytes (with ultrastructural intracytoplasmic lamellar inclusion bodies) is an important histopathologic finding. Lung, liver, skin, nerve and other organs can be affected, and may be dose dependent. DDX includes Legionnaires’ disease, Wegener’s granulomatosis, inflammatory pseudotumor, clear cell neoplasm. Possible mechanisms include induction of phospholipidosis, immune-mediated hypersensitivity, free-radical toxicity.

Take home message:
ALD is life-threatening, can be prevented, may not be recognized in the nodular form and may be misdiagnosed, however, if clinicians and pathologists recognize its existence, the pathologist may be able to suggest the correct diagnosis even if the history of Amiodarone administration is not provided.


Purpose:
Analysis of cases to more clearly identify the clinical and histologic features of PC of the lung. PC is defined as “poorly differentiated nonsmall cell lung carcinoma (NSCLC), namely squamous cell carcinoma, adenocarcinoma or large cell carcinoma, containing spindle cells and/or giant cells, or a carcinoma consisting of spindle and giant cells along, and the pleomorphic component should comprise at least 10% of the neoplasm”.

Methods:
Review of 3322 patients with primary lung cancer in National Cancer Center Hospital, Japan, that were treated surgically. 70 cases were determined to be PC. All cases had H&E, PAS and VVG. Tumors were classified according to the WHO histologic classification. Tumor components recorded (adenocarcinoma, SCCA, large cell carcinoma, spindle cell carcinoma, or giant cell carcinoma). Lymphatic permeating, tumor necrosis, interstitial spread of tumor and pulmonary metastases were recorded. Pathologic staging was performed according to the Union Internationale Contre le Cancer (UICC) scheme. Clinical information was obtained.

Results:
Incidence of 2.2% of all patients that underwent surgical resection for primary NSCLC during the period Male predominance, clear association with smoking Poor prognosis after resection, disease free interval much shorter Most PCs accompanied by pleural and vascular invasion Of 68 cases, adenocarcinoma in 34 cases, SCCA in 11, large cell in 23. Pathogenesis of sarcomatoid component unclear; 2 opposing hypotheses.
Massive coagulation necrosis was an independent prognostic factor for disease-free survival – poorer outcome, may need systemic therapy in addition to surgical resection.

Take home message:
Large review of pleomorphic carcinoma with close look at statistical survival curves.


Purpose:
Investigation of a large number of SFT to evaluate prognostic role of de Perrot classification staging system, p53 expression, presence of abnormalities involving several tumor-promoting genes, growth factor receptor and protein kinases.

<table>
<thead>
<tr>
<th>TABLE 1. Staging System of Pleuro-pulmonary Solitary Fibrous Tumor According to de Perrot et al. 80</th>
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</thead>
<tbody>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage 1</td>
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<tr>
<td>Stage 2</td>
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<tr>
<td>Stage 3</td>
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<tr>
<td>Stage 4</td>
</tr>
</tbody>
</table>

Malignancy at histology was assessed according to the conventional criteria by England et al. 36
*England et al. 36

Methods:
88 cases of completely resected pleuropulmonary SFT from a hospital in Italy and a hospital in France.
Clinicalopathologic parameters analyzed: clinical data, surgical data, radiographic appearance, tumor stage, histologic data.
Tumor cellularity subdivided into 3 categories: keloid-type, mixed/conventional-type, and sarcoma-type.
IHC: CD34, bcl-2, CD99, cytokeratins, p53, PDGFR-a, PDGFR-b, MET, EGFR.
FISH for SYT gene rearrangement, DNA extraction for several different exons.

Results:
Correct diagnosis of SFT reached in 76% of cases using transthoracic FNA, suggesting that this is a useful diagnostic procedure.
De Perrot staging system is a reliable prognostic indicator with a highly significant correlation with sessile appearance, high mitotic rate, tumor cellularity and pleomorphism, necrosis, size >10cm and high p53 expression.
Malignant SFT strongly express p53, an independent parameter significantly correlated with reduced OS and DFS.
Loss of CD34 expression and CK positivity have been seen in malignant SFT and associated with a dismal outcome. No cases showed SYT gene rearrangement, useful with ddx of synovial sarcoma.

**TABLE 4. Results of Immunohistochemistry**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Patients (N = 88)</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>CD34</td>
<td></td>
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<tr>
<td>Positive</td>
<td>85</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
</tr>
<tr>
<td>Bcl-2</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>83</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
</tr>
<tr>
<td>CD99</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>78</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
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<tr>
<td>CKs</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>85</td>
</tr>
<tr>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>88</td>
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<tr>
<td>CD117</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>85</td>
</tr>
<tr>
<td>PDGFR-α</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>86</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>76</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
</tr>
<tr>
<td>c-met</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>85</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
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<tr>
<td>p53</td>
<td></td>
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<tr>
<td>High expression</td>
<td>18</td>
</tr>
<tr>
<td>Low expression</td>
<td>70</td>
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<tr>
<td>SYT rearrangement at FISH</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>88</td>
</tr>
</tbody>
</table>

CKs indicates cytokeratins; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; PDGFR, platelet-derived growth factor receptor.
Consistent immunoreactivity for MET and PDGFR (a and b), which support the idea that the tumor originates from pericytes or mesenchymal pericyte-like cells. No mutations were detected in the tested exons of c-kit, EGFR, c-met, BRAF, PDGFR-a genes. Two cases showed PDGFR-b mutations.

Take home message:
A few useful markers for SFT when the dx is synovial sarcoma or mesothelioma. The PDGFRs are receptor tyrosine kinases (RTKs) and may have a possible therapeutic role in the future.

II. Articles for Notation


Purpose:
To investigate the utility of MASH1 in differentiating pulmonary small cell carcinoma from Merkel cell carcinoma. MASH1 (also called ASCL1) is a transcription factor that is crucial for neuroendocrine differentiation.

Methods:
30 cases of Merkel cell carcinoma and 59 cases of pulmonary small cell carcinoma were reviewed. IHC was performed on the paraffin-embedded tissue for TTF-1 and MASH1.

Results:
49/59 (83%) small cell carcinomas were positive for MASH1 (nuclear staining).
43/59 (73%) small cell carcinomas were positive for TTF-1 (nuclear staining).
0/30 Merkel cell carcinomas were positive for MASH1
1/30 Merkel cell carcinomas were positive for TTF-1
The sensitivity of MASH1 in distinguishing small cell carcinoma from Merkel cell is 83%; the specificity is 100%.
The sensitivity of TTF-1 as above is 73%; specificity is 97%.

<table>
<thead>
<tr>
<th>Table 1 Immunohistochemistry results for Merkel cell carcinoma and small cell carcinoma of the lung</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
</tr>
<tr>
<td>Small cell carcinoma of the lung</td>
</tr>
</tbody>
</table>

0 indicates no staining; 1+, 1–25% tumor cells reactive; 2+, 25–50% tumor cells reactive; 3+, 50–75% tumor cells reactive; 4+, ≥75% tumor cells reactive.
Take home message:
MASH1 is a useful adjunct for the diagnosis of small cell carcinoma of the lung, especially when the ddx is Merkel cell carcinoma. Small study. This differential doesn’t come up a lot, thankfully.


Purpose:
Determination if CRMP5 can be used as a diagnostic or prognostic indicator in patients with primary lung neuroendocrine (NE) tumors.

Methods:
164 cases were reviewed (123 thorax neuroendocrine tumors and 41 randomly selected non-neuroendocrine tumors). Cases were reclassified by two independent pathologists as typical or atypical carcinoid, large cell neuroendocrine tumors or small cell lung tumors. IHC performed – synaptophysin, chromogranin A, CD56, CRMP5. QRT-PCR and Western blot analysis was performed on tumors and normal lung to compare CRMP5 expression.

Results:
Normal lung negative for CRMP5
3/41 carcinomas (non-neuroendocrine) stained for CRMP5
24/46 low grade NE tumors were negative for CRMP5
22/46 low grade NE tumors were positive for CRMP5
71/72 high grade NE tumors were positive for CRMP5 (98.6%) CRMP5 mRNA levels correlated with protein expression in NE carcinoma CRMP5 expression in 34 lymph nodes mets matched that in the corresponding biopsy specimen.

<table>
<thead>
<tr>
<th>TABLE 1. CRMP5 Expression in Primary Lung Carcinoma</th>
<th>CRMP5 Expression</th>
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<tbody>
<tr>
<td></td>
<td>(+ +)</td>
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<tr>
<td>Non-neuroendocrine lung carcinoma (n = 41)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (n = 22)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma (n = 12)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Large cell carcinoma without neuroendocrine features (n = 7)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Low-grade neuroendocrine lung carcinoma (n = 46)</td>
<td></td>
</tr>
<tr>
<td>Typical carcinoid (n = 31)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Atypical carcinoid (n = 15)</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>High-grade neuroendocrine lung carcinoma (n = 72)</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma (n = 54)</td>
<td>54 (100%)</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma (n = 4)</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Combined small cell carcinoma (n = 7)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>Combined large cell neuroendocrine carcinoma (n = 7)</td>
<td>6 (85.7%)</td>
</tr>
</tbody>
</table>

Percentages calculated by rows reflect the distribution of each type of tumors according to CRMP5 expression. CRMP indicates collapsin response mediator protein.

Take home message:
CRMP5 expression helps to differentiate between low grade and high grade NE tumors. CRMP5 is not expressed in NE cells or other cells in the normal adult lung.
Understanding of the signaling pathway that control the growth and differentiation of these cells may be an approach to new therapies.


**Purpose:**
Correlation of the histopathologic classification of mesothelioma in the initial biopsy specimen and the specimen after extrapleural pneumonectomy.

**Methods:**
At MD Anderson Cancer Center, 75 cases of pleural mesothelioma were identified that underwent extrapleural pneumonectomy in an 18 year period. The original biopsy slides or report was reviewed. The EPP specimens were reviewed without knowledge of the original biopsy. Recorded were classification of tumor (epithelioid, sarcomatoid, biphasic, or lymphohistiocytoid), mitotic count, nuclear atypia, and presence of necrosis.

**Results:**
21 cases were reclassified after EPP (17 epithelioid and 4 sarcomatoid) as biphasic. Sex, histologic type and postoperative treatment were significantly associated with disease specific survival (DSS) statistically. After model selection, only histologic type and postoperative treatment were significantly associated with DSS. Only postop treatment was significantly associated with recurrence-free survival (RFS). No significant association of tumor stage with DSS or RFS.

**Take home message:**
A number of these cases are reclassified after EPP, so treatment planning should not be done on limited tissue samples.


**Purpose:**
To evaluate the pathologic and molecular features of LDCT-detected lung cancers, including K-ras mutations.

**Methods:**
Evaluation of 89 LDCT-detected lung cancer resections of patients who underwent annual LDCT, aged >50 y/o, smokers. Compared with 89 consecutive lung cancers matched for confounding factors. Repeat cancers – tumors occurring in the annual repeat LDCT screening of the second year when the previous CT scan was unremarkable.
Results:
Screening cancers (those detected on LDCT) are full-blown carcinomas despite their earlier detection and less advanced clinical stage. The screening cancers were earlier stage, better differentiated, less vascular invasion or pleural infiltration, less necrosis. 29% of the adenocarcinoma nodules had K-ras mutations.

Take home message:
Earlier detection of these cancers is better. They are smaller, less invasive and less aggressive than repeat cancers.


Purpose:
To analyze the major components of the pulmonary ECM in cystic lung light chain deposition disease (CL-LCDD) to determine the influence of metalloproteinases (MMPs) by comparison with other cystic lung diseases.

Methods:
Review of 4 cases of CL-LCDD and comparison with 3 cases of LCH and 3 cases of LAM.
Special stains for elastic, fibrillar collagen and basement membranes were used. IHC and immunodetection was performed for MMPs (TIMP-1 and -2).

Results:
Complete and diffuse loss of elastic fibers in CL-LCDD involving the alveolar walls and small airways and vessels. There was less a degree of loss of type IV collagen and collagen fibers. There was high expression of MMPs by macrophage giant cells. The authors suggest that the decrease in elastic fibers may account for the cyst development. In LCH, basement membranes had disappeared in the cyst wall.
In LAM, each smooth muscle cell in the cyst wall was lined by its own basement membrane and collagen fibers were few.
Take home message:
Small study, but interesting and helpful results if your differential includes these entities.


Purpose:
Study of 157 former denim sandblasters in Turkey to ascertain the frequency of silicosis, to better characterize the extent of the disease and to obtain data about the working conditions.

Methods:
Standard questionnaire to find basic demographic information, exposure duration, work place, time at work, etc.
Personal interview to gather additional information on working conditions.
PFTs.
CXR – posteroanterior

Results:
77/145 (53.1%) of subjects were diagnosed with silicosis; most had worked in more workplaces for a longer duration, as foremen and had a longer latency period.
131 subjects were symptomatic (83%)(dyspnea).
Take home message:
The epidemic of silicosis in this population may be underestimated. Effective measures to prevent the disease process must be undertaken.


Purpose:
Study of 7 cases of anthrocofibrosis to suggest it is a previously unrecognized complication of anthracotic lung diseases.

Methods:
Series of 7 patients who presented to a hospital in England between 1993 and 2007. Medical records were reviewed. Most cases had bronchoscopy; some with biopsy.

Results:
Bronchoscopy reveals anthracotic pigment and narrowing of airways, “coal tattoos”. Biopsies showed pigment laden macrophages, dense acellular collagenous fibrotic material, chronic inflammation.

Take home message:
Anthrofibrocosis appears to be a fibrotic reaction within the airways. There is a possible correlation between it and TB. This is a previously unrecognized complication of anthracotic lung diseases.


Purpose:
Review of ultrastructural abnormalities of respiratory cilia.

Methods:
TEMs reviewed of patients (n=128) with abnormal respiratory cilia from 1983-2007. Specimens included bronchial or nasasl turbinate brushings. Motility and cell viability was assessed. At least 50 cross sections were examined by TEM on each case.

Results:
The most frequently encountered abnormality was truncation or absence of inner or outer dynein arms (71%). In primary ciliary dyskinesia (PCD), most of the cilia are abnormal; in secondary ciliary dyskinesia (SCD) only a minority are abnormal. Few structural defects are specific for PCD or SCD.
The absence of dynein arms and a high percentage of eccentric or absent central pairs is thought to be specific for PCD.

Take home message:
A decent review of ultrastructural abnormalities of cilia, for those of us who occasionally get asked to interpret the EMs.


Purpose:
Observation of morphology, determination of a useful classification system and investigation of involvement of APC/B-catenin pathway in pulmonary artery intimal sarcomas (PAS).

Methods:
All PAS were pulled from the author’s files (18 cases).
IHC – cytokeratin, EMA, vimentin, desmin, factor VIII, CD34, SMA, HMB45, Cyclin A, Cyclin D1, S100, ki-67, B-catenin.
LOH analysis at the 5q2.1 gene locus was performed.
Sequence analysis for B-catenin and APC performed.

Results:
All specimens had a polypoid intraluminal tumor mass in the main artery or pulmonary trunk extending distally along the branches of the pulmonary arteries.
Neoplasms categorized into 4 subtypes: epithelioid, myxofibrosarcoma-type, MFH-type, malignant hemangiopericytoma-like and malignant inflammatory myofibroblastic tumor-like.
Consistently vimentin positive
EMA, Factor VIII, CD34, HMB45, S100 negative
Allelic loss in the APC gene locus in 4/14
No mutations in the B-catenin gene (exon 3) although 14 cases showed B-catenin cytoplasmic positivity on IHC
Cyclin D1 positive cases had significantly greater OS and EFS

Take home message:
Alterations of the Wnt/B-catenin pathway do not appear to be involved in the pathophysiology of PAS.


Purpose:
Presentation of right atrial angiosarcoma with lung involvement.
Methods:
29 y/o African male with chest pain, SOB and hemoptysis. CT of chest showed filling defects of RLL, L lingual and LLL pulmonary arteries. Small nodules were seen bilaterally with small mediastinal nodes. A month later, a moderate-sized pericardial effusion with right ventricular collapse. VATS lung biopsy showed vessels filled with angiosarcoma.

Results:
Presentation of a rare case of cardiac angiosarcoma with multiple metastatic lung deposits and tumor emboli.

Take home message:
Don’t forget to include this in your differential diagnosis of metastatic lung tumors with embolic disease.


Purpose:
Report and study of a 43 y/o woman with FAP and adenocarcinoma of the lung with attempt to identify factors involved in carcinogenesis.

Methods:
RUL lobectomy was performed where tissue was obtained. IHC for surfactant apoprotein (SP-A), TTF-1, and B-catenin were performed. APC, MYH, p53, K-ras and EGFR genes were amplified on PCR. FISH was performed for EGFR.

Results:
The tumor was a mixed adenocarcinoma with a papillary and a BAC component. Both components were positive for TTF-1 and SP-A suggesting that this was a primary lung tumor.
No somatic mutation or chromosomal deletions were found in APC exons; nor was the APC gene methylated. B-catenin was positive in the tumor and in the non-cancerous tissue.
No mutations in p53, K-ras or EGFR were found. No EGFR gene amplification was found.
No microsatellite instability was identified.
A chromosomal aberration on the SNP microarray was found, suggesting that this may be involved in the carcinogenesis.

Take home message:
This tumor was unlike the other tumors that were reported (2 previous cases). Interesting, but not very useful.

Purpose:
Presentation of a case of pulmonary epithelioid hemangioendothelioma mimicking mesothelioma with aggressive clinical behavior.

Methods:
37 y/o male presented with severe upper back pain. CT showed a 4cm solid hilar mass which was locally advanced and unresectable. Work up showed no evidence of metastatic disease. Biopsy showed an infiltrative tumor composed of epithelioid and spindle cells arranged in clusters, strands and trabeculae in a cellular fibrous and dense hyalinized collagenous myxoid stroma. IHC showed strong positivity for vimentin with focal positivity for AE1/AE3, CD31, CD34 and FLI-1. Tumor was negative for Factor VIII related antigen, EMA, CK7, CK20, CK5/6, calretinin, WT-1, thrombomodulin, D2-40, BER-EP4, CEA, TTF-1, SMA and RCCA marker.

Results:
Epithelioid hemangioendothelioma.
Differential diagnosis included mesothelioma, adenocarcinoma (lung primary), metastatic carcinoma, sarcoma with epithelioid features, epithelioid hemangioendothelioma.

Take home message:
Case of PEH with unusual presentation and challenging pathology. The use of IHC was helpful in this case.


Purpose:
Case report of a rare neoplasm with an unusual presentation.

Methods:
48 y/o female had routine physical examination and CXR showed a 2 cm nodule with numerous tiny nodules in the right lung. Biopsy showed a sclerotic lesion with chronic inflammation. Wedge resection was performed. Nodules were composed of round to cuboidal cells in papillary, solid or sclerotic patterns. A cystic lesion was present. Surface cells were positive for TTF-1, EMA, pan-CK, HMW-CK, CK7. Stromal cells were positive for TTF-1, vimentin, PR, and EMA. Chromogranin A, synaptophysin, ER, p63 and CD34 were negative.

Results:
Sclerosing hemangioma with adjacent mucinous lesion that represented reactive hyperplasia of bronchial or bronchiolar epithelium (mucinous adenomatous hyperplasia).
Take home message:
Presentation of a rare neoplasm with an unusual presentation.


Purpose:
Correspondence with presentation of two cases of combined sclerosing hemangiomas and tumorlets. These patients had bilateral disease.

Take home message:
This combination of pathology should be in the differential diagnosis of patients with multiple bilateral pulmonary nodules.


Purpose:
Investigation of stem cell marker expression in SCLC as well as adult and fetal respiratory epithelium.

Methods:
64 SCLC cases, 40 cases with normal bronchial epithelium, 3 cases with squamous metaplasia, 6 cases with proximal bronchi and 21 cases of normal fetal lung were reviewed.
IHC – PODXL-1, Bmi-1, Oct4, AP2gamma, p53, WT1, CD31, p63

Results:
PODXL-1 and Bmi-1 were expressed in most SCLC.
PODXL-1 is expressed in fetal lung

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Immunohistochemical expression of stem cell marker PODXL-1, Bmi-1, and p53 in SCLC (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>PODXL-1–reactive</td>
</tr>
<tr>
<td>Positive</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Weak</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Immunohistochemical expression of PODXL-1, Bmi-1, and p63 in fetal (n = 21) and normal adult bronchial tissue (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase of lung development</td>
<td>PODXL-1</td>
</tr>
<tr>
<td>Pseudoglandular phase (5-17 wk)</td>
<td>1% of stromal cells, dot like</td>
</tr>
<tr>
<td>Canalicular phase (18-26 wk)</td>
<td>Clustered epithelial cells, especially deep pockets, proximal bronchi and trachea, dot like</td>
</tr>
<tr>
<td>Saccular phase (26-38 wk)</td>
<td>Clustered epithelial cells, especially deep pockets, proximal bronchi and trachea, dot-like</td>
</tr>
<tr>
<td>Normal bronchial tissue</td>
<td>No expression in normal bronchial epithelium</td>
</tr>
</tbody>
</table>
Take home message:
PODXL-1 staining cells in lung morphogenesis underscores the hypothesis that there is a possible histogenetic link between SCLC and multipotent airway epithelial cells. Bmi-1 expression is a result of Shh signaling (plays a pivotal role in normal lung development, airway repair and SCLC proliferation.


Purpose:
To find evidence for characteristic molecular changes and protein expression patterns according to the EGFR mutational status in adenocarcinoma of the lung.

Methods:
120 patients with lung adenocarcinomas, 70 of which had BAC components. Mutations of EGFR gene were analyzed by nested PCR and other molecular methods. IHC for EGFR, ErbB3, VEGF

Results:
EGFR mutations were detected in 20/120 tumors. Tumors with BAC differentiation had more frequent EGFR mutations compared to those without. All tumors displayed numerical chromosomal alterations; EGFR mutated tumors carried more mutations on chromosomes 7, 17, 21 and losses on chromosome 8. EGFR-mut positive tumors showed significant VEGF expression, suggesting relevant induction of angiogenesis.

Take home message:
EGFR mutations appear to be linked to a variety of chromosomal imbalances in lung adenocarcinoma. The increased VEGF expression may be useful in therapeutic remedies in the future.


Purpose:
Exploration of DNA variants in the promoter region and coding sequences of E-CAD in samples, along with presentation of evidence for promoter-hypermethylation and defective expression of E-cad and their association with tumorigenesis or primary non-small cell lung cancer.

Methods:
Used 17 human NSCLC cell lines and 95 pairs of NSCLC tumor and corresponding normal peritumoral tissues
Mutation and methylation analysis was performed, along with RT-PCR qualitative and quantitative analysis, Western blotting and IHC (E-cad)

Results:
Defective expression of E-cad is explained by promoter methylation. Expression of E-cad was lower in poorly differentiated tumors than in well-diff tumors. -160C/A polymorphism has increased risk for developing NSCLC
Potential therapeutic strategy for lung cancer is to return the methylated promoter to nearly normal level after treatment with a demethylating agent.

Take home message:
Possible new treatment strategy and screening test (?) for NSCLC


Purpose:
Determination of Pdcd4mRNA suppression in squamous cell lung carcinomas, and study of alterations in Pdcd4 mRNA and effect on Pdcd4 protein level.

Methods:
Tumor (27) and adjacent non-cancerous lung tissues were obtained between May 2004 and Nov 2005.
Six cell lines were also studied.
Pdcd4 transcript levels were measured by PCR, antibodies were made, Western blot and IHC were performed on the cases.

Results:
In NSCLC statistically significant transcriptional suppression of Pdcd4 was seen in SCCA.
In 14 samples of SCCA loss of Pdcd4 protein was not found. In the cell lines there was variation in the mRNA level and the amount of protein found.
Pdcd4 protein is abundant in SCCA
Restoration of Pdcd4 expression is not a good strategy to treat these tumors because there is a significant amount of protein present in the tumor cells.

Take home message:
A scientific article that may steer one in a different direction for therapeutic strategies.


Purpose:
Examination of expression of Dvl family members in NSCLC as well as comparison to B-catenin expression in the progression of lung cancers.
Methods:
113 NSCLC cases between 2003 and 2006; 39 of which had available nodal mets. Evaluation of Dvl family members by IHC, RT-PCR of cultured cells

Results:
Dvl family members are expressed in lung cancer tissues and associated with clinicopathological factors
Incidence of positive expression was higher in adenocarcinomas vs SCCA
Expression of these proteins is associated with a poor tumor differentiation
Expression of Dvl in nodal mets is increased and correlated with B-catenin expression
Exogenous expression of Dvl-1 or Dvl-3 strikingly increased the invasive ability of the cells
Normal adult bronchial and alveolar epithelium showed no expression of Dvl

Take home message:
These Dvl proteins may have a role in invasion and metastases and may be a potential therapeutic target for lung cancers.


Purpose:
To study the implication of IPF on surgical results of pulmonary resection for primary lung cancer.

Results:
Acute postoperative exacerbation of IPF has a high mortality and its occurrence is difficult to predict
The surgical treatment of primary lung cancer is effective in patients with stage I lung cancer and IPF.

Take home message:
Interesting study to assist the surgeon on decision making on their patients with IPF and lung cancer.