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## Pleural Disease

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Case Reports


I. Articles for Discussion


**Background:** Suster and Moran have raised several questions regarding the applicability of the WHO system and its practical use in the daily practice of pathology. They suggest a new classification scheme including thymoma, atypical thymoma, and thymic carcinoma. The purpose of the study is therefore to evaluate the WHO classification scheme of thymomas.

**Methods:** A search of PubMed from 1999-2007 was performed. 15 retrospective cohort studies were found that included 2,192 patients with thymomas (min. 5-year follow-up).

**Results:** Only one study in the literature evaluated interobserver agreement of “B” subtypes of thymomas, which was only 0.49. In addition, by comparing the studies and the proportions of thymomas reported, the authors argue that the interobserver reliability of classifying thymomas by the WHO scheme is not reliable.

No statistically significant difference in survival rates were found between patients with thymoma types A, AB, and B1. Only statistically significant differences in survival were found between thymoma types A, AB, and B1 and either B2 or B3 thymomas.

**Discussion:** Significant heterogeneity exists between these studies, including treatment for patients with the same stage disease (surgery ± radiotherapy ± chemotherapy).

Simplification of the WHO classification of thymomas into three types based on differences in survival: A/AB/B1, B2, and B3. This would potentially improve interobserver reliability and provide significant prognostic value.

Since it is difficult for any thymoma study to perform a prospective collection of data over ten years with a significant number of cases, the authors suggest that organization of a national or international registry of thymoma patients (data repository and tissue bank) be constructed for the use of future meta-analysis studies.
Background: Several studies have recently raised into question the prognostic value of stratifying thymomas into stages I and II based on findings that show no significant prognostic differences between them. Bedini et al has suggested an alternative staging system based on 123 thymoma patients combining stages I and II into a “locally restricted” group, compared to “locally advanced” patients with stage III or stage IVa.

Masaoka staging system (1980s):
Stage I – Completely encapsulated tumor without microscopic invasion of the capsule
Stage II-I – Macroscopic transcapsular invasion into adipose tissue/mediastinal pleura
Stage II-II – Microscopic transcapsular invasion
Stage III – Invasion of neighboring organs
Stage IV – Metastasis to the pleura or distant organs

Methods: A search of PubMed from 2001-2006 found 21 retrospective case series, each with at least 10 patients with thymomas that were staged and followed for a 5-yr min.

Results: These studies were quite heterogeneous. All Stage I and II pts received thymectomy, but some stage I pts also received postop radiation therapy, whereas some stage II pts didn’t. Tumor capsule sampling was variable. None evaluated the influence of interobserver and intraobserver variability. None reported statistically significant differences in disease free survival and overall survival in Stage I and II thymoma pts.

Discussion: This study included pts with stages I and II thymomas from a wide geographic distribution. No statistically significant difference was identified in prognosis between stages I and II thymomas. Numerous confounders of the data were present. Complete surgical resection of thymomas was found in 19 of the 21 studies to be an important prognostic indicator (applicable to intraoperative consultation). Significant 5-year survival differences were identified between pts with Stage I and Stage III thymomas, and Stage I and Stage IV thymomas.

Since differentiating between stage I and II thymomas doesn’t provide prognostic information, should capsular invasion even be reported? A study at the University of Pennsylvania (Singhal et al) reviewed 167 thymomas and found no therapeutic benefit for radiation therapy in patients with completely resected thymomas in Stages I or II.

Suster and Moran suggest using “favorable vs. unfavorable” to classify thymomas based on capsular invasion, completeness of resection, and WHO histologic subtype. However, until more data can be collected, they propose collapsing the Masaoka staging system into three categories: I-III [completely excised (R0), incompletely excised (R1), and grossly present at the margin (R2)].

Given the difficulty in performing a prospective randomized study, and the difficulties with meta-analysis on the current studies available, the authors propose developing an international registry of thymoma patients.
Background: In 2002, the ATS/ERS identified NSIP as a separate entity, but there was concern that this was a “wastebasket” category. NSIP was originally designed to classify a group of pts with interstitial pneumonia that could not be classified into one of the other idiopathic interstitial pneumonias. The purpose of this study was to determine if NSIP is a distinct entity, and to identify the clinical, radiologic and pathologic characteristics (CRP).

Methods: 305 cases of potentially NSIP were reviewed among a panel of 6 pathologists with them rendering a definite, probable, possible, or definitely not NSIP diagnosis. Radiologic and clinical data were also reviewed in a blinded fashion and classified similarly. Cases were excluded if they had established clinical, radiologic, or pathologic criteria for: UIP, COP, hypersensitivity pneumonitis, airway disease/bronchiolitis, RB-ILD, DIP, or DAD. Cases that had known exposure to drugs or airborne antigens or met rheumatologic criteria for collagen vascular disease prior to presentation were also excluded. Pts who developed collagen vascular disease after the initial diagnosis were included.

Results: Of the 305 cases, 112 were excluded, with either inadequate or contradictory biopsy material, HRCT examination or clinical history. Out of the remaining 193 cases, 67 were identified as definite, (n=17) or probable (n=50) NSIP. Refer to table 4 for histologic features. Patients with NSIP that fit the criteria outlined in this study have a 5-year survival of 82.3% and a 10-year survival of 73.2%, significantly better than UIP.

Discussion: Idiopathic NSIP is a distinct clinical entity:
1. Clinical presentation: female, breathlessness and cough, 6 to 7 months duration, never smokers, sixth decade of life, restrictive ventilatory defect.
2. HRCT: bilateral, symmetric, lower lung reticular opacities with traction bronchiectasis. Lower lobe volume loss is usually diffuse or subpleural.
3. Pathology: mild to moderate interstitial chronic inflammation (cellular); dense or loose interstitial fibrosis with uniform appearance and preservation of architecture (fibrosing). Absent or inconspicuous: granulomas, eos, hyaline membranes, fibroblastic foci, honeycombing.
4. Prognosis: 5-year mortality rate less than 18%.

Interestingly, 1/3 of cases in which a definite or probable pathologic diagnosis of NSIP was made, the consensus CRP diagnosis was not NSIP. Several studies suggest that pts with cellular NSIP pattern have a more favorable prognosis than pts with fibrosing NSIP pattern. In this study there was insufficient data to address this question.

Implications for practice: CRP correlation is critical for the diagnosis of idiopathic NSIP. In cases in which CT or biopsy are believed to show features of NSIP but there is some concern for hypersensitivity pneumonitis, the term “NSIP pattern” is appropriate.

Future work: Incidence and prevalence, sexual and ethnic predilection, whether NSIP associated with collagen vascular disease behaves differently, etc.

**Background:**
- Classification of lung Ca continues to undergo evolution; most emphasis has been placed on dx of BAC and molecular implications of EGFR and RAS mutations. But BAC accounts for only a minority of ADCA and EGFR/RAS mutations are only present in 30-60% of all ADCA.
- Therefore, comprehensive approach to histologic subclassification of lung adenocarcinoma with genetic correlations is needed.

**Methods:** 100 Surgically resected primary lung ca (MSKCC). Two pathologists reviewed all slides and were classified using revised 2004 WHO system: mixed, acinar, papillary/micropapillary, BAC, solid, miscellaneous variants. Tumors were classified according to major histologic subtype with estimates in increments of 10% of additional components.

- Specific features noted:
  - small papillary tufts lying free within alveolar spaces or encased within walls of connective tissue with no fibrovascular cores = micropapillary tumors.
  - numerous intra-alveolar tumor cells disqualified a case from being BAC
  - simple papillary structures were accepted in BAC but not 2° or 3°.

Tumors analyzed for KRAS and EGFR mutations by CISH, IHC and gene expression analysis using microarrays and clustering techniques.

**Results:** 94% of ADCA were of mixed subtype (no pure BACs!). Papillary, acinar, solid, and BAC comprised major histologic subtypes in decreasing order of frequency. Not surprisingly the most common pattern present in any amount was acinar followed by micropapillary, solid and BAC.

Correlations with histologic features:
- Tumors with major solid subtype showed higher grade, worse prognosis and a weak correlation with more advanced stage.
- Tumors with major BAC and papillary subtypes had weak correlation with lower grade but there was no association between percent of BAC and papillary components.

Correlation with EGFR and KRAS mutations
- Lack of smoking was strongly correlated with EGFR mutation; tumors with major papillary subtype were strongly correlated with EGFR mutation (including micropapillary).
- No strong correlation between subtype and KRAS status. EGFR FISH, EGFR ICH or phosphorylated EGFR ICH showed no correlation with histologic subtype.

Gene expression analysis:
- Correlations with specific clusters of genes showed
  - Cluster 1: correlated with less smoking, major papillary subtype, micropapillary subtype and EGFR mutation
  - Cluster 2: strong correlation with major BAC subtype and weaker correlation with smaller size and lower grade
  - Cluster 3: correlated with large tumor size, heavy smoking, solid subtype, poor differentiation and less TTF1 staining

Survival: patients with major solid subtype had worse survival. Stage 1 patients with major papillary subtype had 96% 5-year survival compared with 72% for other subtypes.

**Discussion:** Authors adequately address potential problems with their study including sampling (7 slides per case). Interesting that BAC histology did not correlate with EGFR mutations but no pure BACs were present in the study (rather surprising).

Authors show the potential value of reporting overall percentage of all histologic subtypes of lung carcinoma which results in meaningful correlations with clinical and molecular features including smoking status, gene profile clustering and EGFR mutations. Future studies are obviously recommended.
Comments: I really liked this paper. The authors were very careful about defining subtypes and offered guidance for the broader community which I found very helpful. The paper contains a lot of images, data, tables and graphs. I highly recommend reading this paper.

**Background:** Idiopathic pleuropulmonary fibroelastosis (IF) has only been described in one report (Frankel, et al. Chest 2004;126:2007-13). The authors report 2 more cases.

Case 1: A 51-year-old woman with progressive dyspnea and cough.
PMH: Emphysema, reflux; meds: oxygen, tiotropium bromide, budesonide, and formoterol fumarate, montelukast, theophylline, prednisone, omeprazole, amlodipine, diltiazem and atorvastatin.
PFTs: Severe obstruction with mild gas transfer defect. Chest x-ray showed biapical fibrotic changes with some nodular components with tenting of right hemidiaphragm and upward retraction of right hilum.

Case 2: A 59-year-old woman with dyspnea and cough.
PMH: Hiatal hernia, asthma, possible asbestos exposure as a child. FCC lymphoma treated with fludarabine, CHOP, rituximab, and a stem cell transplant Meds: prednisone, inhaled fluticasone/salmeterol and tiotropium bromide, mesomeprazole and duloxetine hydrochloride;
PFTs: Mod restr. with mild gas transfer deficit. CXR: biapical pleural fibrotic changes.

Both of their patients developed postoperative pneumothoraces. The authors speculate that the pleural changes may be responsible in some way.

**Pathology:** Unfortunately there is minimal pathologic description given for these cases.
Case 1: “abundance of short, curly and randomly oriented elastic fibers in a thickened interstitium”.
Case 2: “abundance of elastic fibers in addition to collagen fibers with above transitioned from fibroelastosis to unaffected normal lung parenchyma”; thumb-nail view shows an “extraordinarily thickened pleural cap with sparing of the adjacent lung parenchyma”.

**Discussion:**
IF apparently differs from other IIPs in that the fibrosis shows a predominance of elastic tissue. “The unique differentiating pathologic features of IF are intense, predominantly elastic fibrosis of the visceral pleura, particularly of the upper lobes, which consists of accumulations of short, curled and randomly oriented elastic fibers”. The entire pleura appears as a homogeneously thick elastic band. The elastosis is seen extending into the alveolar walls that insert in the pleura and beyond, although in our cases it never occupied the whole extent of the sections obtained. The transition from thickened, elastic alveolar walls to normal parenchyma was sharp.

Comment: The authors discuss the differential with UIP, but interestingly not with apical cap lesions, which to my eye these appear to resemble more than any “interstitial disease”.
I don’t really understand whether this represents an entity or not, and how it might be different from an apical cap lesion. (none of Yousem’s patients had restriction, 2 presented with hemoptysis).
II. Other Major Articles of Note- Non Neoplastic


This is a radiology based paper. Using a combination of high resolution CT scan and pulmonary function tests, a simple staging algorithm was identified for patients with systemic sclerosis. **No attempt is made to characterize the nature of the pathology** in these patients but the authors conclude that “an easily applicable limited/extensive staging system for FSc-ILD based on combined evaluation with HRCT and PFTs provides discriminatory prognostic information”. Interestingly the staging system was predictive of mortality for all scores with prognostic separation higher for practitioners than trainees.

2. Editorial

Strange C, Seibold JR. Scleroderma lung disease: “If you don’t know where you are going, any road will take you there”. Am J Respir Crit Care Med. 2008;177:1178-9.

These authors recommended adopting the proposed staging system.

This represents the third articles in a series “Pulmonary Hypertension: Basic Concepts for Practical Management”. Given the fact that Jay was one of the authors I decided to take a look.

Although this study purports to report on pulmonary hypertension in “interstitial lung disease”, in fact, it really only focuses on pulmonary hypertension in sarcoidosis, systemic sclerosis and IPF. It was a bit surprising that they failed to mention pulmonary hypertension in the setting of lung of PLCH. Nonetheless, this is a reasonable (although fairly short) review of pulmonary hypertension in patients with some kinds of pulmonary fibrosis.

Topics covered:

- Basic aspects of pulmonary fibrosis and PH
- Prevalence and burden of PH in ILD
  - Sarcoidosis
  - Systemic sclerosis
  - Idiopathic pulmonary fibrosis
- Diagnosis and Staging of PH in ILD
  - Radiology
  - Echocardiography
  - Natriuretic peptides
  - Right heart catheterization
  - Pulmonary function test
  - Histology (“histology is not required to make a diagnosis of PH and obtaining a lung biopsy for the sole purpose of assessment of PH in ILD is therefore generally discouraged”).
  - General diagnostic approach
- Treatment of PH in the context of ILD
- Lung transplantation
- Future directions
III. Other Major Articles of Note- Neoplasia


Background: The majority of Australia’s lung cancer occurs in current or former tobacco smokers, but there have been very few studies which have analyzed the contribution of asbestos exposure to the development of lung cancer in this population.

Methods: Asbestos bodies were quantified in patients undergoing resection for primary lung cancer.

Results and Conclusions: The majority of patients with primary lung cancer at this Queensland Hospital had detectable asbestos fibers in resected lung tissue but fiber burden was generally low. Therefore, the contributory role of this low-level exposure remains uncertain.

Comment: The authors did not comment on whether any of the patients had concurrent fibrosis which, of course, is potentially significant.

**Background:** Nodular ground-glass opacities (NGGOs) in patients with extrapulmonary cancers is not known. The purpose of the study was to investigate the clinical significance of pulmonary NGGOs in this group of patients and to develop a computerized scheme to distinguish malignant from non-malignant NGGOs.

**Methods:** Fifty-nine pathologically proven NGGOs in 34 patients with a history of extrapulmonary cancer were identified. CT characteristics were identified in artificial neural networks (ANNs) constructed to distinguish benign from malignant NGGOs.

**Results:** 82.4% were determined to be malignant (24 primary adenocarcinomas, 16 primary bronchioloalveolar carcinomas). The rest represented atypical adenomatous hyperplasia (14), focal fibrosis (4), and benign inflammatory nodule (1). No cases of metastasis presented as NGGOs. Neural networks showed an excellent accuracy rate in discriminating benign from malignant NGGOs.

**Conclusion:** Pulmonary NGGOs in patients with extrapulmonary cancers are very often primary lung cancers. ANNs may be useful to distinguish benign from malignant NGGOs.

**Comment:** I thought this was an interesting study given the pathologic findings.
IV. Pleural Disease


The authors present eight cases of DPMM occurring in children <15 years of age, 5 girls and 3 boys. All presented with ascites. None had a history of direct or indirect asbestos exposure and no pleural disease was documented. Possible predisposing factors such as a history of radiation were not addressed so presumably such a history was lacking in this group.

Among the group 6 were papillary, 2 epithelial and 1 biphasic.

Follow-up limited. Four patients were alive 12-18 months after initial diagnosis and one died two years after diagnosis.

The discussion has a nice table listing the previous 12 reported cases.

Comment: Good reference to have for these unfortunate cases!

**Background:** Definitive diagnosis of MM can be difficult based on morphology alone. Homozygous deletion of 9p21, the locus harboring the p16 gene, has been reported as the most common genetic alteration in MM. Recent studies demonstrate this alteration may be useful for differentiating benign from malignant mesothelial proliferations in cytology specimens.

The diagnostic utility of homozygous 9p21 deletion was assessed by FISH in paraffin-embedded tissue.

**Results:**

**Table 1. Summary of p16 immunohistochemical and FISH analysis**

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<th>FISH p16 deletion (%)</th>
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<td>Pleural mesothelioma</td>
<td>32/52 (60%)</td>
<td>35/52 (67%)</td>
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<tr>
<td>Peritoneal mesothelioma</td>
<td>6/21 (29%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>34/40 (87%)</td>
<td>0/40 (0%)</td>
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Abbreviations: FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry.

**Figure 1.**

Frequency of homozygous deletion of 9p21 and loss of *p16* expression in benign mesothelial proliferations and malignant mesothelioma. (IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PLM, pleural malignant mesothelioma; PM, peritoneal mesothelioma; RM, reactive mesothelial cells).

**Conclusions:** 9p21 homozygous deletions assessed by FISH may be helpful for differentiating MM from reactive mesothelial proliferations.

The title makes this sound like a paper looking at patients with IPF in association with lung cancer; however, it is mainly a study designed to look at the risk factors for developing pulmonary toxicity due to gefitinib. Age, performance status, smoking and preexisting chronic ILD were important risk factors for developing “acute ILD” in patients being treated with chemotherapy for NSCLC.

Comment: Might be a useful paper when dealing with consult cases. Histology not defined, however. ? DAD

This is a review and covers current knowledge about genes expressed in non-small cell lung cancer. There is a nice figure describing the genetic alterations in apoptotic signaling in lung cancer for those of you who might be lecturing on such a topic.
V. Case Reports


First case report of a patient developing diffuse alveolar hemorrhage on alemtuzumab being given as part of an immunosuppressive protocol following renal transplantation. Diagnosis was based on BAL, not biopsy.

Case report of thoracic splenosis, with predisposing factor having been an automobile accident at the age of 9.

A case of chronic eosinophilic pneumonia.

A case of LIP associated with common variable immunodeficiency.

The discussion is quite good.

Hopefully none of you need anything more than the title…but the answer to this pulmonary puzzle is…Erdheim-Chester disease.