Articles for Discussion


**Background:** 5-10% of asthma patients have “severe” disease, but this is poorly understood and pathologic studies have been largely limited to autopsy studies of patients dying in status asthmaticus. This study was undertaken to evaluate the pathology in patients with severe asthma.

**Methods:** Pts identified and evaluated at the “difficult asthma clinic” at the UPMC. 19 patients with CT scans showing no parenchymal abnormalities and severe/atypical asthma who did not improve or worsened over time despite conventional therapy were recommended for VATS biopsy.

**Results:** 10/19 patients who underwent VATS biopsies 2007-2011 had a combination of asthmatic small airway changes with non-necrotizing interstitial and airway centered granulomas on pathology. All were oral corticosteroid dependent and had no evidence for other respiratory disease. One patient was on omalizumab but none on methotrexate. One patient had Crohn disease. 9/10 had significant sinus disease by CT scan. All patients had chest CT within 10 months of surgery. 5/10 had normal CT; the other 5 CTs revealed nonspecific bronchiolar dilation (n=5); bronchiolar wall thickening (n=4); patchy predominantly subsegmental air trapping (n=2); subsegmental atelectasis (n=2); tree-in-bud opacities (n=1) and small mucosal nodules in central airways (n=1). Focal or extensive bronchiectasis, thoracic lymph node enlargement and consolidation were absent. Peripheral blood eosinophilia was present in most and high despite systemic corticosteroids. Multiple unilateral wedge biopsies were taken from all patients and features shown below.

![Pathology images](image)

Patients were treated with a variety of other agents (azathioprine, methotrexate, infliximab, mycophenolic acid) resulting in a decrease of CS doses.

**Conclusion:** These data suggest that a subset of severe “asthmatic” patients manifest granulomatous pathology which the authors term “asthmatic granulomatosis”. Identification requires thoracoscopic biopsy but alternative approaches to therapy appear to lead to improved outcomes.

**Comment:** Interesting report with pathology findings reviewed by TVC and Jody Wright. Sounds like a new disease to me!
- Still concerned about the one patient who had Crohn disease but that still leaves 8 patients with no apparent etiology.

- The authors do not comment on the pathology in the other 9 patients which I found odd.

**Background:** IgG4-related disease is a relatively newly recognized fibro-inflammatory condition characterized by

a. Tendency to form tumefactive lesions at multiple sites
b. Dense lymphoplasmacytic infiltrate rich in IgG4 positive plasma cells
c. Storiform fibrosis
d. And often, but not always, elevated serum IgG4 concentrations

The nomenclature continues to evolve. An international consensus symposium was held 10-2011 comprising 35 disease-related global experts, invitations based on contributions to the literature.

- Purpose of this statement is to provide practicing pathologists with guidelines for the diagnosis of IgG4-related disease; guidelines not intended to supplant proposals for organ-specific diagnostic criteria.

Although the combination of histopathologic and immunohistochemical stains can provide strong support for IgG4-RD, careful correlation with clinical scenario is required.

Three major Histopathologic features of IG-RD: (1) dense lymphoplasmacytic infiltrate; (2) fibrosis arranged at least focally in a storiform pattern; and (3) obliterative phlebitis. Other features (1) phlebitis without obliteration of the lumen and (2) increased number of eosinophils.

In most instances “a confident pathological diagnosis of IgG4-RD requires the presence of two of three major histologic features”. *Exceptions exist in lymph node, lung, salivary and lacrimal glands where storiform fibrosis and obliterative phlebitis may be absent.*

IgG4-to-IgG ratio: IgG4+/IgG+ plasma ratio is more powerful than counting IgG4+ plasma cells alone. Greater than 40% has been suggested as a comprehensive cutoff in any organ; authors address several caveats.

**Semiquantitative analysis of IgG4:**

a. IgG4 and IgG cells can be counted using printed photomicrographs at 40x objectives
b. Direct counting can be performed under microscope
c. Count hotspots
d. It may be difficult to implement precision in “everyday practice”

Proposed terminology:

a. Histologically highly suggestive of IgG4-related disease
   - Dense lymphoplasmacytic infiltrate
   - Fibrosis, usually storiform in character
   - Obliterative phlebitis
b. Probable histologic features of IgG4-related disease
   - Cases with only a single feature, typically dense lymphoplasmacytic infiltrate with some IgG4 cells
   - Needle biopsies
   - Meningeal and cutaneous tissue: published data for IgG4-related disease in these organs is limited
   - Patients with histologically probable IGRD require additional evidence
     ➢ Serum IgG4 > 135 mg/dl
➢ Other organ involvement by either radiologic or pathologic examination
c. Insufficient histopathologic evidence of IgG4-related disease

**Conclusion:** Diagnosis of IgG4-RD requires collaboration. Diagnosis rests predominantly on morphologic appearance in tissue IgG4 counts and IgG4/IgG ratios are of secondary importance.

**Comment:** A good summary of IgG4-RD with good comments regarding differences across organ sites.

**Background:** Recent advances in genetic characterization of liposarcomas (LPSA) indicates three histogenetic types.
- Well-differentiated/atypical lipomatous tumor: lacks metastatic potential in the absence of dedifferentiation. This group along with de differentiated LPSA have giant ring and microchromosomes containing amplified sequences of chromosome region 12q13-15, detectable by FISH for genes such as MDM2, CDK4, and CPM.
- Myxoid LPSA/round cell LPSA: 95% characterized by t(12; 16)(q13; p11) resulting in formation of FUS-DDIT3 (CHOP) fusion gene with 5% showing variant t(12; 22)(q13; q12), forming an EWSR1-DDIT3 fusion gene.
- Pleomorphic LPSA contains complex numerical and structural chromosomal abnormalities similar to other high-grade sarcomas.

**Purpose:** To report large clinicopathologic series of primary LPSA in mediastinum using current classification scheme and ancillary techniques when appropriate.

**Methods:** Consult files (ALF and TVC) and MCR files 1952-2011; seven cases from consult files and 17 from MCR. (2/3 of patients in the Mayo Clinic files of LPSA represented metastases).

**Results:** 24 cases (13 male, 11 female), 15-73 years of age, (mean, 53y). Anterior mediastinum – 7, posterior mediastinum – 6, middle mediastinum – 3, superior mediastinum – 2, inferior pleural space – 1, extensive involvement of thorax and multiple mediastinal compartments – 5.

22/24 patients treated by surgical resection or debulking (2 inoperable).

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<td>Well-differentiated/dedifferentiated LPSA</td>
<td>58%</td>
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<tr>
<td>Myxoid liposarcoma</td>
<td>8%</td>
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<tr>
<td>Pleomorphic liposarcoma</td>
<td>29%</td>
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<td>Unclassified</td>
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Follow-up: 8-252 months. Death: 1/6 well-differentiated, 1/4 dedifferentiated, 5/7 pleomorphic, 2/2 myxoid.

Unusual variants: myxoid and smooth muscle differentiation in well diff tumors, myxoid LPSA with extensive adipocytic differentiation and highly myxoid pleomorphic LPSA resembling myxoid LPSA. Highlights importance of molecular techniques for appropriate classification.

**Discussion:** primary mediastinal LPSA are rare

Mediastinal LPSA differ from retroperitoneal counterparts in which overwhelming majority are well-differentiated/dedifferentiated type.

The distribution of LPSA types in the mediastinum is unusual compared to soft tissue subtypes.

Careful histopathologic evaluation is important in diagnosis. A number of unusual features seem to be present in mediastinal liposarcoma including myxoid change in well-differentiated liposarcoma, presence of smooth muscle differentiation, the presence of extensive adipocytic differentiation in myxoid liposarcoma, and highly myxoid pleomorphic liposarcoma mimicking myxoid liposarcoma. Genetic testing in such cases may be indicated and helpful.

Comment: Great paper for reference of an unusual tumor, but one to keep in mind!

At the outset although the title says that the authors are describing “ciliated adenocarcinomas of the lung” they really aren’t describing carcinomas with cilia but rather carcinomas arising from ciliated epithelium.

**Background:** One potential pathway for adeno-carcinogenesis in the lung is the AAH/AIS/MIA/invasive sequence arising in the periphery of the lung (so-called terminal respiratory unit adca; adcas comprised of cells with type 2 Clara cell or bronchiolar cell morphology). These authors describe a second potential pathway comprised of changes in bronchial and bronchiolar columnar cells; hence, their term ciliated “adenocarcinomas” also known as “non-terminal respiratory unit type adenocarcinoma (NTRUA)”.

This may be the pathway followed by mucinous tumors arising in CPAM for example.

**Methods:** Among all resected lung ca’s (2005 to 2010) definitive adcas were selected and reviewed. For some unintelligible reason (the authors really should have had someone whose first language was English help them with the manuscript) they did not review cases which were high grade and TTF-negative.

157 total cases reviewed and divided into two groups: (1) terminal respiratory unit carcinomas comprised of Clara cells, type II pneumocytes, or bronchiolar cells, based on dome-shaped protruding cytoplasm and (2) NTRU adenocarcinomas comprised of bronchial surface epithelium, mucous cells or goblet cells with flat cytoplasmic surfaces or mucus-containing cytoplasm. The presence of mucous columnar cell change was evaluated in both groups. EGFR/KRAS status was also performed.

**Results:** 121/157 = terminal respiratory unit morphology. Mucous columnar cells absent; TTF almost always positive, diffuse and intense.

36/157 = NTRU.

- Six pure mucinous AIS, 1 colloid, the remainder mixtures of acinar, micropapillary, papillary, solid and lepidic but tumor cells were “goblet cell”, mucous columnar cell type or bronchial surface cell type. TTF weak and never over 50% of tumor cells.

In terminal respiratory unit type EGFR 46%, KRAS 7%. In NTRU: EGFR 8%, KRAS 24%.

**Mucous Columnar Cell Change:** In 24/36 cases of NTRU ADCA, transitional foci from normal ciliated columnar epithelium to mucous columnar cells was observed with varying degrees of nuclear atypia up to AIS. A grading system is proposed (see Table 2).

**Pathologic and Clinical Features of Adenocarcinoma Arising from Mucous Columnar Cell Change**

- Acini frequently larger than terminal respiratory unit type.
- Papillary and micropapillary occasionally mixed with acinar type.
- Lepidic growth pattern not evident.
- Tumor cells appear to be of 3 types: mucous producing, oncocytic and goblet cell (least common).
- 10/36 cases showed marked honeycomb change (although the authors do not comment on whether these tumors arose in the setting of UIP/IPF).

**Survival:** There were no survival differences between patients with terminal respiratory versus non-terminal respiratory type carcinomas.

**Discussion:** Summary of their findings includes

a. Adcas arising from mucous columnar cell change appear to have transition foci from normal ciliated columnar cells to mucous columnar cell metaplasia and dysplasia, mucous containing or eosinophilic cytoplasm and cells are TTF negative.

b. Patients with these tumors are frequently smokers (data not shown above)

**Comment:** An interesting hypothesis and plausible based on my experience.
Articles for Notation

Diffuse Lung Disease


This represents a very brief case report largely in the form of images. It is interesting to note that there is a moderate amount of lymphoid hyperplasia present in the lung biopsy.


Foscarnet (the pyrophosphate analog trisodium phosphonoformate foscarnet) has been used to treat ganciclovir-resistant CMV infection. Prior reports on toxicity focus on presence of renal toxicity with or without crystal deposition. This case report highlights findings in a 42-year-old man.

**Methods:** autopsy of patient dying of CMV reactivation. Lungs showed evidence of chronic airway rejection (obliterative bronchiolitis) and mild acute cellular rejection. In addition, the lungs showed multiple disseminated birefringent structures surrounded by granulomatous inflammation with multinucleated giant cells. Similar crystals were identified in the kidney, epicardium, pericardium, myocardium and esophagus.

**Comment:** first case report of this unusual complication.

Case report with images of a woman with iron tablet disintegration within the airway resulting in necrosis of airway wall and marked iron deposition (iron pill aspiration).


Case report of a woman with lymphangioleiomyomatosis. Reasonable brief review of the current diagnostic criteria from the ERS.

Comment: not sure why case reports like this keep getting accepted.


Case report of a woman with granulomatous auto-inflammatory disease (AUID) associated with a rare nucleotide-binding oligomerization domain-containing protein-2 (NOD2) gene mutation.

Case report: previously healthy woman with psoriasis developed recurrent skin lesions, dyspnea on exertion without cough and bilateral pleural effusions. These resolved with prednisone but her dyspnea returned after discontinuation of prednisone.

Serologic testing for a systemic autoimmune disease was negative including ANA, ANKAs, etc. Genetic testing of the NOD2 gene for mutation by DNA PCR and DNA sequencing was performed and it was positive for heterozygous R703C variant of the NOD2 gene. Imaging showed bilateral lower lobe interstitial infiltrates with ground-glass attenuation without adenopathy.

Transbronchial biopsy showed focal interstitial chronic inflammation and ill-formed nonnecrotizing granulomas without infection. VATS showed diffuse chronic lymphoplasmacytic infiltrates with lymphoid aggregates and numerous multinucleated giant cells. A skin biopsy also developed interstitial granulomatous dermatitis.

Discussion: Blau’s syndrome is an autosomal dominant auto-inflammatory disease in children characterized by granulomatous dermatitis, inflammatory arthritis, and uveitis. It may occur in “atypical form” which may be the same thing as early-onset sarcoidosis. Blau’s syndrome is linked to the NOD2 gene mutation. The authors hypothesize that this might represent an adult-onset Blau’s syndrome characterized by recurrent dermatitis, inflammatory arthritis, periodic fevers and the presence of granulomatous pulmonary disease.

Comment: Fascinating case report; clearly we’ve got a lot to learn about granulomas in the lung as this case, the case report about pathology of severe asthma and foscarnet therapy exemplify.


In a retrospective evaluation pulmonary hypertension was identified in approximately 20% of patients with LAM. Pathologic assessment of explanted lung in 5 patients demonstrated “pronounced vascular remodelling” with involvement of pulmonary arterial walls by PEComa cells. The authors do not comment, however, on how these changes might be related to the presence of pulmonary hypertension.
Infection


The authors examine the relationship between the pathologic pattern in CMV infection (diffuse alveolar damage versus interstitial inflammation/fibrosis, versus a combination, and expressions of transforming growth factor beta 1 (TGF-β1, integrin β6 (ITGB6) and interleukin 8 (IL-8)).

Double immunohistochemistry of CMV antigen and cellular markers showed that epithelial tropism was associated with a diffuse alveolar damage (DAD) pattern (CMVp-DAD) while stromal tropism was associated with a predominantly interstitial inflammation/fibrosis (IIF) (CMVp-IIF) or a combination of DAD and IIF (CMVp-complex). TGF-β1 expression was higher in mixed DAD and inflammation groups than in those with DAD alone. Diffuse IL-8 up-regulation and strong expression were both present in CMV-infected pneumocytes and stromal cells in CMVp-IIF, especially those with marked neutrophil infiltration.

The authors conclude that TGF-β1, ITGB6 and IL-8 in CMV infected pulmonary cells play an important role in development of diverse histologic patterns associated with this infection.


Case report of a lung nodule secondary to atypical mycobacteria in a patient with AIDS.
Miscellaneous


Since this editorial is fairly short, I would suggest reading it if you are at all interested in the relationship between small airways, pathology and obstruction in COPD. It turns out that contrary to what had been thought, there is a significant reduction in the presence of terminal bronchioles to 10% of control values in persons with severe centrilobular emphysema and 25% of control values in patients with panlobular emphysema.


A 29-year-old woman with IgG4-related pleuropericarditis which responded to corticosteroid therapy.


Interesting report based on observations done in patients with thoracoamniotic shunts used as treatment for type 1 CPAM.

**Background:** Thoracoamniotic shunting has been performed and is now considered a routine way to treat macrocystic CPAM with large cysts, CPAM volume ratio greater than 1.6 or hydrops fetalis, prior to 34 weeks gestation. The authors observed the presence of squamous metaplasia in the cyst epithelium of 5/8 patients treated prenatally with thoracoamniotic shunting and 0/6 patients were not treated with this procedure.

**Comment:** The histologic findings of less interest perhaps than the fact that this type of surgery is now considered routine.
Neoplasms


This represents an editorial highlighting the article by Camidge et al (below) comparing clinical characteristics of patients with ALK-positive NSCLC to those of patients with EGFR or KRAS mutations or triple negative (so called) lung cancer patients. The authors discuss the various benefits and drawbacks of types of testing (IHC versus FISH versus RT-PCR).


**Background:** FISH, ALK probes consistently show rearrangements in <100% of tumor cells in ALK-positive NSCLC. Increased copy numbers of fused and rearranged signals also occur. The authors explore correlations between the percentage of ALK-positive cells and signal copy number and their associated response to ALK inhibition.

**Methods:** Ninety ALK-positive NSCLCs.

Percentage of positive cells, pattern of positivity, and copy number of fused, isolated red and green signals were recorded. Thirty patients had received crizotinib.

**Results and Conclusions:** There was a strong association between increased copy number of key ALK signals and percentage of positive cells suggesting that <100% positive rate of cellular reactivity in ALK-positive tumors is due to technical and not biologic factors.


**Background:** the genetic alterations in sarcomatoid carcinoma are largely unexplored. This makes it difficult to use target therapy in patients with this type of tumor.

**Methods:** EGFR, HER2, KRAS, p53, CTNNB1, BRAF and PIK3CA mutations were assessed by various methods in 20 pleomorphic carcinomas, two pulmonary blastomas and one carcinosarcoma. 51 consecutive metastatic lung adenocarcinomas were used as controls for FISH and IHC assays of ALK gene.

**Results:** no rearrangements of ALK were detected but amplification was identified in 5/23 (22%) surgical specimens and paired biopsies. p53, KRAS, and CTNNB1 mutations accounted for 30%, 22%, and 4% of cases, respectively, with no significant relationship with ALK amplification. No mutations for EGFR, HER2, BRAF, or PIK3CA gene were observed.

**Conclusion:** ALK gene amplification is a nonrandom and clonally related event in a subset of pulmonary sarcomatoid carcinoma but its biologic relevance requires further investigation.

A review by many of our European colleagues which covers:
- Molecular basis of ALK inhibition therapy
- Effectiveness and safety of ALK inhibition therapy
- Detection of ALK gene rearrangements
- Tissue management
- Standardized tissue and cell processing
- Clinical diagnostic tests
- Clinical tests including IHC, FISH, PCR
- Proposal for external quality assessment program
- Testing algorithm
- Conclusions


Review article with the following issues addressed:
- Clinical and diagnostic features
- Clinical significance of molecular testing
- Considerations for testing
- Specimens and specimen handling
  - Specimens with molecular prioritization
  - Rebiopsy specimens for resistant testing
  - Specimen selection
- Selection of reference laboratory
- Emerging molecular markers
- Conclusion

Comment: Although I have not heard of the authors, they are at the University of Colorado where we have begun sending out tumors for ROS1 typing.


Background: EGFR mutation analysis is critical for guiding treatment of lung adenocarcinoma.

Methods: 108 cytologic samples were evaluated using TheraScreen EGFR29 kit.

Results/Conclusions: mutations were detected in 22 (23.9%) of 92 amplified samples, 9 containing less than 200 cancer cells, and 4 with less than 50% cancer cells. These findings indicate that cytologic specimens are adequate for EGFR testing when a highly sensitive assay is used, even if they are paucicellular or not optimally fixed.


Background: MicroRNA (miRNA) has been found to be critical in tumorigenesis through post-transcriptional modification and is considered to be a potential biomarker for cancer diagnosis and treatment.
**Methods:** the expression pattern of three miRNAs (miR-21, miR-155 and let-7a) were evaluated to determine their potential role in the diagnosis of pulmonary neuroendocrine tumors by quantitative RTPCR; typical carcinoid (19), atypical carcinoid (6), large cell neuroendocrine carcinoma (19), and small cell carcinoma (19).

**Results:**
- Expression levels of miR-21 and miR-155 were significantly higher in high grade neuroendocrine carcinomas than in carcinoid tumors ($P < 0.001$).
- Expression level of miR-21 in carcinoid tumors with lymph node metastases was significantly higher than in carcinoid tumors without lymph node metastases ($P = 0.01$).

**Conclusions:** The authors suggest that expression patterns of miR-21 and miR-155 may be adjunctive diagnostic tools in the diagnosis of pulmonary neuroendocrine tumors.


A case report in CPC format of diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH).


**Methods:** an evaluation of 37 cases of small cell carcinoma arising outside the lung.

**Results:** TTF-1 reactivity noted in 9/25 cases of small cell carcinoma (bladder, cervix, liver, esophagus, prostate and rectum); synaptophysin was positive in 20/25; 34βE12 positive in 8/25.

**Conclusions:** the TTF-1 expression can be seen in tumors from a wide variety of locations, particularly when they have small cell morphology and synaptophysin can be a negative in a significant proportion of small cell carcinomas.


Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is being increasingly used for the diagnosis and staging of patients with lung cancer.

**Methods:** three pathologists independently reviewed specimens from 60 patients who underwent EBUS-TBNA. Smears, H&E and IHC specimens were reviewed without the use of a “control” resection specimen.

**Results:** almost perfect agreement was seen for distinguishing small cell from NSCLC. However, interobserver agreement for EBUS-TBNA specimens was moderate for the determination of NSCLC subtype. Smear (Kappa = 0.095), H&E (Kappa = 0.278), and IHC (Kappa = 0.564). Perfect agreement was seen when all three observers were confident of diagnoses made on IHC specimens.

**Conclusions:** clinicians should be aware of the degree of pathologists’ confidence in the tissue diagnosis prior to commencement of targeted therapy!

**Background:** this study evaluated the FNA and histology in 602 patients with lung cancer.

**Methods:** comparison between cases classified before and after immunohistochemistry more widely used.

**Results:** cytohistologic agreement was achieved in approximately 94% of cases.

- There was a significant decrease in the percentage of cases not subtyped after the introduction of targeted therapy (35.07% versus 24.57%; P <.01). Interestingly, an average of three markers was used but the number of antibodies did not influence overall success in subtyping. More than half of the cases were not subtyped even after IHC (these turned out to be poorly or undifferentiated neoplasms in the surgical specimens). Other factors which influenced the ability to subtype are explored.

**Conclusions:** specific subtyping can be achieved in a high proportion of lung FNAs with high accuracy.


**Background:** this is a second report on long-term outcome of patients treated by limited resection for pulmonary ground-glass opacities 2 cm or smaller (from 1998 to 2002).

**Methods:** enrollment criteria included:
- Pulmonary peripheral nodule less than 2 cm
- Diagnosis or suspected diagnosis of T1N0M0 carcinoma with ground-glass opacity and lack of evident pleural indentation or vascular conversion on HRCT
- Limited resection performed with intraoperative frozen section
- If nodule confirmed as Noguchi type A or B with resection margin greater than 1 cm, the incision was sutured and patient followed
- Median surveillance was 10 years

**Results:** in a total of 50 enrolled patients
- Noguchi type A, 2
- Noguchi type B, 23
- Noguchi type C, 15
- AAH, 5
- Fibrosis, 4
- Granuloma, 1

No recurrences within first 5 years.

Four patients developed either margin recurrence or metachronous primary disease.

**Conclusions:** of 26 patients, adenocarcinoma developed at more than 5 years. Authors conclude that 5 years in not sufficient and that limited resection should still be done only in a trial setting even for GGO type lesions.
Background: Neuropilin-2 is a co-receptor for vascular endothelial growth factor family members and a blockade of neuropilin-2 is able to suppress lymphogenous metastasis in preclinical models. The aim of the study was to validate a protocol for the evaluation of neuropilin-2 expression in situ by comparing in-situ hybridization, western blotting, and mRNA expression levels.

Methods: Immunohistochemistry was performed on normal tissue and whole sections.

- Primary non-small-cell lung carcinoma – 79
- Primary breast carcinoma – 65
- Colorectal cancer – 79
- Metastatic tumors – 52

Results: Neuropilin-2 was observed in lymphatic and blood vessels from all normal and malignant tissues examined. In addition, 32% of primary non-small-cell lung carcinomas, 15% of breast, and 22% of primary colorectal carcinomas showed tumor cell expression. Fifty-five primary and nine secondary malignant melanomas were also examined for neuropilin-2 expression by ISH. All showed vascular expression and 85% of melanomas showed tumor cell expression.

Conclusions: Neuropilin-2 in the majority of lung, breast and colorectal cancers is confined predominantly to blood vessels suggesting that any pharmacokinetic use of neuropilin-2 blocker can be expected to affect the vasculature.

Background: Pemetrexed (Pem) is an inhibitor of thymidylate synthase (TS) and has shown efficacy in the treatment of non-small-cell lung cancer. The authors explored TS expression in NSCLC biopsy specimens and correlated results with those identified in resection specimens.

Results: When their robust scoring system is used TS expression levels in NSCLC biopsy specimens appears to correlate with TS expression in the whole tumor.

Conclusions: Further studies are needed to determine whether high or low TS expression in NSCLC is of predictive value and whether it allows for selection of patients who may benefit from Pem therapy.

Background: This study examined the clinicopathologic characteristic of subcentimeter adenocarcinomas, especially those which showed evidence of early invasion.

Methods: Among 595 adenocarcinomas, 66 subcentimeter carcinomas were identified and treated in a variety of ways (lobectomy, segmentectomy, and wedge resection).

Results: 36 were invasive and 30 noninvasive (representing AIS).

- Invasive carcinomas were significantly more frequent in males than females, and included 20 tumors MIA) and 16 tumors with >5 mm invasion, 5 of which had no lepidic growth portions (entirely invasive carcinoma).

- Approximately half of the invasive carcinomas had no localized fibrous area >1 mm in diameter (LFA), and showed histologic features of invasive carcinoma with localized lepidic growth including MIA.
(Noguchi's type C).

- Invasion was sometimes difficult to detect in these carcinomas. High-grade nuclear atypia was always associated with invasive carcinomas and aided the diagnosis. The authors also try to be very clear about how they define invasion and highlight the use of elastic tissue stains and other IHC markers to identify early invasion.

- Invasive carcinoma with >5 mm invasion was significantly associated with presence of metastasis in sensitivity analysis in patients followed for more than two years.

- Compared with adenocarcinomas of 11-20 mm in diameter, subcentimeter carcinomas included significantly more AIS, fewer entirely invasive carcinomas, and fewer invasive carcinomas with LFA.

**Conclusions:** Familiarity with patterns of invasion is important to accurately diagnose patients.

**Comment:** For those struggling with how to identify invasion in small tumors, this is a helpful paper and one I recommend reading.


Case report of a papillary adenoma of type 2 cells in which the authors explore the expression of multiple growth factors. Tumor cells expressed fibroblast growth factor (FGF) 2 and produced 350 times more FGFR2IIIb messenger RNA than did nontumorous lung. The quantity of keratinocyte growth factor mRNA in the tumor tissue was twice that of nontumorous lung. Also, there appeared to be dysregulation of FGFR2IIIb transcription in the tumor.

According to these findings it appears as though over-expression of FGFR2IIIb plays an important role in tumorigenesis. Because of associations of FGFR with lung carcinogenesis complete resection of the adenoma is suggested.

**Comment:** although the patient was young I have doubts about whether this 3 cm tumor truly represents a papillary adenoma. See photo below and judge for yourself.
Desmoid tumors are clearly rare in the lung and chest wall. Interestingly, among eight patients reported in this series, one of eight occurred in the thoracic wall.

The title is a double entendre. It turns out that the authors are studying patients with desmoid tumors who have been treated by radiation rather than a study of desmoid tumors caused by therapeutic radiation.

Bottom line is that in this small series, the data suggest that histologic alterations attributable to ionizing radiation are minimal. Therefore, the presence of cytologic features of malignancy in this setting require careful examination and consideration of a post-radiation sarcoma. This developed in one of their eight patients.


**Background:** there have been few series analyzing clinicopathologic predictors of outcome in a large series.

**Methods:** 103 patients with resected solitary fibrous tumor (SFT), excluding meningeal tumors were evaluated including primary soft tissue (79), pleural (31), and sinus (4).

**Results:** A risk stratification model was proposed

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<td>Age</td>
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<tr>
<td>&lt; 55</td>
<td>0</td>
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<tr>
<td>≥ 55</td>
<td>1</td>
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<tr>
<td>Tumor size (cm)</td>
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<td>&lt;5</td>
<td>0</td>
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<td>5 to &lt;10</td>
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<td>10 to &lt;15</td>
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While small tumors with low mitotic rates were highly unlikely to metastasize, large tumors greater than 15 cm, in patients occurring ≥ 55 years with mitotic figures ≥ 4/10 require close follow-up and have a high risk of metastasis and death.

**Comments:** a paper worth knowing about if you are going to be speaking or signing out cases of solitary fibrous tumors.
Transplantation


Background: grading of rejection in lung biopsies from transplant recipients underwent revision in 2007. The goal of this study was to determine how these revisions affect patient care.

Methods: a web-based survey of pathologists and pulmonologists was used.

Results:
- Some pulmonologists do not interpret pathologic diagnosis of lymphocytic bronchiolitis (as a grade B rejection) resulting in under-treatment.
- Most pulmonologists treat bronchiolitis obliterans differently if the biopsy shows evidence of active mononuclear inflammation (although reporting this is contrary to the 2007 guidelines).

Discrepancies were also identified among pathologists in their interpretation of airway lymphocytic infiltrates, whether eosinophils can be present in BALT and whether airway inflammation represents rejection or infection.

Conclusions: grading and treatment of airway inflammation in pulmonary allografts remains problematic.

Comment: Clarification from the transplant community would be beneficial.

Vascular Disease


Report of two women who develop PVOD soon after the initiation of oral contraceptives. Both patients required lung transplantation to treat their disease.

Comment: A complication worth knowing about for those rare pulmonary vascular disease biopsies.