### Pulmonary Pathology Journal Club

**May 4, 2015 (articles from March 2015)**

Joanne Yi, M.D. and Scott Aesif, M.D.

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**Articles for discussion**


**Background:**

-Biology and outcome of atypical carcinoid (AC) are still not very well known and based on small single-institution studies.

-Available information suggests that patients with AC often present with early stage disease and a surgical resection is the preferred treatment modality; However, the body of literature on AC largely comes from surgical series and therefore remains skewed toward earlier stage disease with overall better outcomes.

-The effectiveness of radiation and/or chemotherapy for AC is unknown, either alone or in adjunct with surgery.

-Author analysis of the Surveillance, Epidemiology, and End Results (SEER) database Program of the NIH to investigate clinical characteristics and outcomes of AC patients

**Methods:**

-SEER program: sponsored by the NIH and collects information regarding cancer incidence and survival from 18 population-based cancer registries that cover approximately 28% of the US population.

-All patients with a dx of lung and bronchus cancer classified according to the ICD-0-3/WHO 2008 criteria between 1973-2010 were identified in the SEER database.

-However, pulmonary AC cases were only available in SEER beginning in 2001, when the standardization in the histologic coding of AC started.

-They identified the cases with this dx and extracted the relevant data using the case listing session of SEER*Stat 8.1.2 software. From that group, patients with an ICD-0-3 histology dx of AC were identified and employed for the primary analysis.

**Results:** 441 of 947,463 (0.05%) patients diagnosed with lung and bronchus tumors in SEER database had AC.
Conclusion and take home message:

- AC is an uncommon tumor and 20% presented with metastatic disease and it occurred more frequently in women.

- Older age, advanced stage, and African American race were identified as negative prognostic factors.

- No survival difference in this study between pts who underwent a sublobar resection vs. lobectomy and more extensive surgeries, even when controlling for stage and age; This finding was consistent with prior SEER studies that had a larger focus on TC.

- Not much is known regarding the tx and outcomes for pts with more advanced stages of AC, as most published date came from surgical series.
**Nunes et al. Nonspecific interstitial pneumonia: Survival is influenced by the underlying cause. Eur Respir J 2015;45:746-55**

**Background:** Idiopathic NSIP may include some cases associated with connective tissue diseases (CTDs) and chronic HP. Emerging evidences indicate that “idiopathic” NSIP is in fact the manifestation undifferentiated CTDs (UCTDs). The aim of this study is to compare the prognosis of NSIP stratified according to the underlying cause (i.e. idiopathic, UCTDs, CTDs, and chronic HP) in terms of survival, response to therapy and long-term functional outcome.

**Methods:** -A retrospective study on consecutive patients with a histological pattern of NSIP by surgical lung bx in a single institution. The same cohort has been used in a previous study for reviewing the prognostic relevance of histological variants in NSIP (Histopathology 2014;65:549-60).

-Dx was made by two pathologists (M. Kombouchner and A.G. Nicholson).

-Clinical, laboratory fx, PFTs and BAL fx at the time of bx were recorded.

-Two radiologists reviewed HRCT taken within 6 mos of HRCT and classified HRCT pattern as “suggestive or consistent with NSIP” or “suggestive of UIP”.

-Standard diagnostic criteria for differentiated CTDs; UCTD when at least one sx suggestive of CTDs and evidence of systemic inflammation in the absence of infection.

-For CHP, they required clinical and radiological evidence of ILD plus history of exposure to an inhaled antigen known to cause CHP and either confirmatory serum precipitins or a lymphocytic BAL.

-Therapeutic response was recorded within 3-6 mos of tx initiation. Long-term functional outcome was evaluated for pts with available PFTs at least 12 mos after their initial assessment. Improvement was defined as a \( \geq 15\% \) increase in diffusing capacity of DLCO% predicted from initial values and worsening defined as \( >10\% \) decrease in FVC or \( >15\% \) decrease in DLCO.

**Results:**

| TABLE 4 | Patient outcomes according to aetiological groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Idiopathic NSIP | UCTD* | CTDs | cHP | p-value |
| Subjects       | 51              | 32    | 29   | 15  |         |
| Duration of follow-up months | 66.7±58.0 | 64.3±49.3 | 67.1±61.7 | 45.8±31.5 | 0.716 |
| Treatment at some point during follow-up | 39 | 26 | 21 | 13 | 0.849 |
| Corticosteroids | 20 | 14 | 12 | 6 | 0.966 |
| Azathioprine    | 12 | 6 | 11 | 4 | 0.352 |
| Cyclophosphamide| 6 | 10 | 10 | 6 | 0.526 |
### Background:

Pleuropulmonary fibroelastosis (PPFE) is not listed as one of the rare IIPs in the 2013 classification of IIPs. PPFE has been described as a pathological phenotype of restrictive allograft syndrome following lung transplantation (Ofek E, et al. Mod Pathol 2013;26:350-6). (Another paper in the same issue of Histopathology (discussion article by Takeuchi et al) reported that it is frequent pulmonary sequelae of hematopoietic stem cell transplantation). Ofek et al has postulated that PPFE is a consequence of DAD. The authors of this paper also hypothesized that other forms of PPFE, idiopathic or secondary, may have an inflammatory or acute lung injury process prior to the development of PPFE. So, they investigated histological evolution in the development of PPFE based on two sequential specimens from 4 patients.

### Methods:

They identified 4 patients during 2006-13 diagnosed as PPFE by surgical bx (n=1) or autopsy (n=3), who also had prior surgical lung bx’s, and the dx of their first bx’ s was not PPFE. Histological findings were reviewed with HE and EVG stains and the histological differences between first and second bx or autopsy were examined. Clinical data and imaging findings during the course were also reviewed.
**Results:** Table 1. Clinical characteristics and laboratory data

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<th>Case 3</th>
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<tr>
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<td>Case 2</td>
<td>Case 3</td>
<td>Case 4</td>
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Take home message: Interstitial inflammation or acute lung injury may be an initial step in the development of PPFE.


Aims: Pulmonary complications have been reported to occur in 70% of patients following haematopoietic stem cell transplantation (HSCT). The spectrum of complications includes constrictive bronchiolitis obliterans (most commonly encountered), lymphocytic bronchiolitis, and veno-occlusive disease. Recently, histologic findings resembling pleuroparenchymal fibroelastosis (PPFE) have been described in HSCT patients. Idiopathic PPFE was established as a new entity in the 2013 American Thoracic Society / European Respiratory Society Idiopathic Interstitial Pneumonia statement. PPFE consists of intense elastotic fibrosis involving the pleura and subpleural parenchyma, predominantly in the upper lobes. Pulmonary function studies have shown a restrictive pattern, and the condition can be progressive and fatal. This study sought to review and identify the histologic features of PPFE after HSCT using a retrospective review of patients who underwent lung transplantation following HSCT.
Results: A total of 20 patients were included in the study. Fifteen patients had chronic graft versus host disease in other organs (skin [9], liver [6], salivary gland [6]). Lung transplantation occurred at a median of 4.6 years (range 1.2-14.8 years) following HSCT. A summary of the histologic findings is provided in Table 2.

Preoperative computed-tomography images were available for 18 patients. In order of prevalence, findings included bronchial dilation (16), mosaic attenuation (16), centrilobular nodules (12), ground-glass opacities (6), and honeycomb change (3). Plueroparenchymal thickening, i.e. areas of subpleural opacity, were present in 13 patients whose imaging was available, and appeared consistently in the upper lung fields and less frequently in the middle and lower lung fields. Histologically PPFE was present in 15 patients and in most cases was found in more than one lobe (usually in all lobes), but was thicker in the upper and middle lobes. PPFE was sharply demarcated from the adjacent normal lung parenchyma, with fibroblastic foci being present at the interface in 10 cases. The authors state that concurrent non-specific interstitial pneumonia (NSIP) was identified in 75% of PPFE cases and was mostly focal with a predominantly lower lung field distribution. The true concurrent nature of the NSIP is unclear based on the numbers provided in Table 2. This is not delineated explicitly by the authors. Similarly, the authors conclude by speculating that PPFE may represent a consequence of persistence, rather than resolution, of intra-alveolar organizing pneumonia, but ultimately concede that the underlying aetiology is largely unknown.


Background and Aims: There exists ambiguity with regard to staging patients with multiple primary lung cancers (MPLC). The goal of the study was to access the prognosis of synchronous (occurring at the same time) and metachronous (occurring at different times) MPLC using a systematic literature review (EBSCO, PubMed, OVID, and Spinger). Guidelines amongst American Joint Committee on Cancer (AJCC), Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC) vary for staging MPLC. AJCC states that when multiple tumors are present in the same organ the T category is based on the tumor with the largest size / extent and multiplicity is denoted in parenthesis, e.g T2(3); however, no guideline is given regarding tumors of differing histology. IASLC guidelines are similar but imply that this classification can be used for tumors of different histology in the same organ. AJCC states that tumors occurring in different organs or metachronous tumors of the
same organ should be staged independently. UICC states that tumors occurring in the same organ but with differing histologies should be staged independently.

**Results:** A total of 22 retrospective studies were extracted from the data bases after applying inclusion and exclusion criteria. All of the studies queried utilized Anatakli et al. diagnostic criteria for diagnosis of a second primary lung cancer – A) different histological conditions or B) same histological conditions with two or more of the following: anatomically distinct, associated premalignant lesion, no systemic metastases, no mediastinal spread, and/or different DNA ploidy. A total of 1796 MPLC patients were identified, including 913 synchronous MPLC and 883 metachronous MPLC. Overall survival (OS) of patient with synchronous MPLC was statistically inferior to patients with metachronous MPLC when starting from the diagnosis of the first metachronous tumor (11 studies), but statistically similar when starting from the diagnosis of the second metachronous tumor (9 studies). OS in patients with MPLC was found to be statistically superior to that of patients with intrapulmonary metastases (3 studies). OS was not statistically impacted when synchronous and metachronous tumors were discriminated for by histology (8 studies). OS was not statistically impacted based on unilateral versus bilateral disease (4 studies).

**Merits and Application:** The study highlights an inherent difference between synchronous and metachronous MPLC in that they document a statistically superior OS for metachronous MPLC when looked at from the initial diagnosis. The finding that there is not a statistically superior OS for metachronous MPLC when looked at from the second tumor diagnosis, may highlight a potential intervention point for improving patient outcomes. The authors suggest that this finding may relate to poor patient physical condition, stressing the need for quality rehabilitation following primary interventions. The authors stress their findings that patient’s with intrapulmonary metastases have statistically poorer OS when compared to MPLC patients; however, these findings represent one of the smallest patient groups examined. Similarly, the methodologies used to identify intrapulmonary metastases varied amongst the included articles. The findings regarding OS based on histology and laterality may be of future use in deriving consensus guidelines for staging of MLPC patients.

**Articles for notation**

**Non-neoplastic**

Stanley et al. What the genetics “RTEL”ing us about telomeres and pulmonary fibrosis. Am J Respir Crit Care Med 2015;191(6):608-610

Editorial for the article below by Cogan et al.

Cogan et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. Am J Respir Crit Care Med 2015;191:646-655
**Background:** Up to 20% of cases of IIP cluster in families, comprising the syndrome of familial interstitial pneumonia (FIP). The genetic basis of FIP remains uncertain in most families. In 2007, mutations in genes encoding the telomerase enzyme were found in up to 15% of families with pulmonary fibrosis (PF). Telomerase has two essential components the telomerase reverse transcriptase (*TERT*), and the telomerase RNA (*TR*). Mutations in *TERT* and *TR* explained the inheritance in the largest subset of cases. Mutations in the telomerase component *DKC1*, and the telomere binding protein TINF2, account for another 1-2% of cases. Now, this study reported mutations in the regulator of telomere length 1 gene (*RTEL1*), in familial PF.

**Methods:** They analyzed exome sequence data from 25 families and then used controls of convenience from the 1,00 Genome and Exome Sequencing Project databases to ensure identifying rare variants. They examined shared variants within families while prioritizing those in telomere genes.

**Results:** In one large autosomal dominant family, they identified heterozygous *RTEL1* mutations that segregated with PF. Through a multi-institutional collaborative effort, they screened 163 additional cases by exome sequencing and found 4.7% of probands carried rare *RTEL* variants that also segregated with the PF phenotype. In some cases, telomere length was documented to be short, similar to telomerase mutation carriers. Probands and unaffected carriers of these rare variants had short telomeres (<10% for age) in peripheral blood mononuclear cells and increased T-circle formation, suggesting impaired *RTEL* function.
**Take home message:** Rare loss-of-function variants of RTEL1 may represent the 5th telomere gene involved in familial PF (see figure above).

**Haggmark et al.** Proteomic profiling reveals autoimmune targets in sarcoidosis. *Am J Respir Crit Care Med 2015;191:574-583*

**Background:** There is no distinct diagnostic marker for sarcoidosis and there is a need to characterize the antibody repertoire in relation to sarcoidosis and potentially related autoantigens. They investigated BAL and serum samples from sarcoid patients along with healthy and diseased control subjects to discover sarcoidosis-associated autoantigens.

**Methods:** Antigen microarrays built on 3,072 protein fragments were used to screen for IgG reactivity in 73 BAL samples from subjects with sarcoidosis, subjects with asthma, and healthy subjects. A set of 131 targets were selected for subsequent verification on suspension bead arrays using 272 additional BAL samples and 141 paired sera. Reactivity to 4 antigens was furthermore analyzed in 22 unprocessed BAL samples from patients with fibrosis and 269 plasma samples from patients diagnosed with myositis.

**Results:** ZNF688 (Zinc finger protein 688), MRPL43 (mitochondrial ribosomal protein L43), NCOA2 (Nuclear receptor coactivator 2), and ARFGAP1 (adenosine diphosphate-riboseylation factor GTPase activating protein 1)

**Take home message:** They found 4 markers associated with sarcoidosis out of 131 selected targets. These proteins may function as autoantigens that may become clinically applicable tests to support the diagnosis.

**Shoemark et al.** Bardet Biedl Syndrome motile ciliary phenotype. *Chest 2015;147(3):764-770*

**Background:** Bardet Biedl Syndrome (BBS) is clinically characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, genital anomalies and renal abnormalities. The phenotype of this genetic condition is thought to occur because of a loss of function in nonmotile primary cilia resulting from an absence of BBS proteins. BBS proteins are located at the base of a cilium, some in a complex called the BBSome, which is involved in the movement of particles in and out of the cilium by a process known as intraflagellar transport. Dysfunction of nonmotile cilia in BBS is well known but ciliopathy affecting motile cilia has not been well known human; murine models has suggested the colocalization of BBS in both nonmotile and motile cilia. The aim of this study was to assess the structure and function of respiratory ciliary dysfunction in a cohort of patients with BBS.

**Methods:** They studied 46 BBS patients (24 men; age ranging from <1 to 48y with average of 22 y) for the clinical symptoms of motile cilia dysfunction and the histology of ciliated respiratory epithelium.
**Results:** Increased prevalence of neonatal respiratory distress at birth (12%), asthma (21%), otitis media (33%), and rhinitis (36%). These symptoms, however, occurred at a significantly reduced prevalence compared with those having known motile cilia dysfunction or primary ciliary dyskinesia (PCD). Respiratory epithelial assessment revealed cellular damage, significant ciliary depletion (60% of ciliary cells), and goblet cell hyperplasia (50% goblet cells). These findings were similar to those with asthma. Surprisingly, motile cilia function and ultrastructure were grossly normal with the exception of occasional unique inclusions within the ciliary membrane.

**Take home message:** Motile ciliary structure and function are essentially normal in BBS patients; however, a small proportion of cilia contain inclusions within the ciliary membrane, unique to BBS on EM.

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**van den Kieboom et al. Nasopharyngeal gene expression, a novel approach to study the course of respiratory syncytial virus infection. Eur Respir J 2015;45:718-725**

**Background:** RSV causes mild infections in the vast majority of children. However, in some cases, it causes severe disease, such as bronchiolitis and pneumonia. Development of severe RSV infection is determined by the host response. Therefore, the main of this study was to identify biomarkers associated with severe RSV infection.

Previous studies showed the gene expression profiles in peripheral blood mononuclear cells represent the subject’s health. Based on the blood RNA profiles of infants, a classification of infants with RSV lower respiratory infection (LRTI) vs. rhinovirus or influenza LRTI was made with 95% accuracy. They used blood samples, which can be limited in pediatric patients. In this study, they assessed the possibility of measuring host gene expression in nasopharyngeal aspirate (NPA) taken from children with
lab-confirmed RSV infections and aimed to identify markers with potential prognostic value for the course of disease.

**Methods and Results:** Nasopharyngeal gene expression was profiled by microarray studies, resulting in the selection of five genes: *ubiquitin D*, *tetraspanin 8*, *mucin 13*, *β-microseminoprotein* and *chemokine ligand 7*. These genes were validated by real time PCR in an independent validation cohort, which confirmed significant differences in gene expression between mildly and severely infected and between recovery and acute patients.

**Take home message:** The combination of pathogen detection and host gene expression analysis in nasopharyngeal aspirates may improve the diagnosis and prognosis estimation of RSV respiratory tract infection.


**Background:** Only minority of LAM cells react with HMB45 Ab, which gives a limited utility in small specimens. HMB45 recognizes a region within the central polycystic kidney disease domain of Pmel17 (also called silver protein and ME20). Another antibody of interest, αPEP13h, recognizes an amino acid sequence in the C-terminal portion of Pmel17 and appears to identify a different spectrum of LAM cells in the lung nodules in LAM. They compared HMB45 and αPEP13h reactivity in LAM. In contrast to HMB45 that recognizes Pmel17 in melanosomal structures in a small fraction of SMA+ LAM cells, αPEP13h recognizes Pmel17 in the cytoplasm and premelanosomes of >82% of LAM cells in 90% of LAM patients. αPEP13h Ab may help in the diagnosis of LAM and other PEComas.

**Methods:** IHC was done on both paraffin tissue and frozen tissue. Frozen tissue was used for double stains with HMB45 and αPEP13h antibodies via IF method. The source of αPEP13h antibody is not given and it was described as “αPEP13h was raised against the polypeptide 647-CKLGENSPLLSGQQV-661”. Thus, it is not a commercially available antibody.

**Results:** HMB45 recognized approximately 25% of LAM cells within the LAM lung nodules, where as αPEP13h identified >82% of LAM cells within these structures in approximately 90% of patients with LAM. While HMB45 reacted with epithelioid but not with spindle shaped LAM cells, αPEP13h identified both spindle and epithelioid LAM cells. HMB recognized Pmel17 in premelanosomal organelles; αPEP13h recognized proteins in the cytoplasm and in premelanosomal organelles. Both antibodies recognized a Pmel17 variant of approximately 50kDa.

**Take home message:** Got αPEP13h antibody?

**Background:** TP63 gene is located on 3q28 and encodes a member of the p53 family of transcription factors. The role of p63 protein in tumorigenesis is not clear. P63 isoforms with N-terminal truncation (ΔNp63) may have either tumor suppressor or oncogenic function, depending on the genes that are transactivated. Mutations in TP63 have rarely been reported including in lung cancer (<4% of NSCLC studied). Most are missense mutations reported with a tumor suppressor activity. These mutations have been described in both squamous cell carcinoma and adenocarcina. TP63 amplification and p63 IHC nuclear positivity in lung cancer is most commonly observed in squamous cell carcinoma and p63 by IHC has been used to differentiate squamous cell vs. adenocarcinoma. Unusually p63 expression in adenocarcinoma is focal but in about 5% of tumors expression is more diffuse. 4A4 clone, commonly used for p63 IHC, does not distinguish between the transactivated and ΔN isoforms of p63, likely explaining the p63 positivity in adenocarcinoma. In contrast, p40 Ab for ΔN isoforms of p63, is highly specific for squamous cell carcinoma and only rarely reported in adenocarcinoma. By NGS analysis of mate-pair DNA libraries, novel chromosomal rearrangements involving TP63 has been identified in 6% of peripheral T-cell lymphomas with poorer overall survival than those without these gene rearrangements. These lymphomas show p63+/p40- IHC profile.

**Methods:** Authors examined the presence of TP63 rearrangement and associated p63/p40 expression of lung adenocarcinoma. NGS was used to identify genomic rearrangements of TP63 in 37 ADCs. FISH using a break apart probe to the TP63 gene region and IHC for p63 and p40 were performed on ADCs with TP63 rearrangements identified by mate-pair sequencing. IHC for p63 and p40 were performed on additional 45 lung ADCs and FISH was performed on all p63 positive cases.

**Results:** TP63 rearrangement was found in 2 ADC specimens from a single patient. The rearrangement of 3q is characterized by fusion of B3GALNT1 at the 3’ intron to TP63. FISH confirmed the rearrangement in both tumors. IHC for p63 was diffuse (>80% of cells +) and p40 was negative. In the validation set, 13 of 44 additional ADCs (1 failed technically) showed p63 positivity and p40 was negative in all. No case showed rearranged of TP63 by a break apart FISH but extra copies of the intact TP63 locus were seen in all 12 cases with the tissue sufficient for FISH (copy number 3-7)

**Take home message:** A novel chromosomal rearrangement involving TP63 in a p63+/p40- lung ADC. p63 positivity is not specific for this rearrangement as 30% of ADCs express p63 without it, but with copy number gain of intact TP63

Boland et al. Intrathoracic peripheral nerve sheath tumors – a clinicopathological study of 75 cases. Hum Path 2015;46:419-425

**Background:** Peripheral nerve sheath tumors (PNSTs) are common in the posterior mediastinum but are rare in other compartments of mediastinum and in the lung or pleura. Authors studied the clinicopathological features of PNSTs occurring in the lung and pleura along with those in the mediastinum.
**Methods:** Cases were found from the consult files of two authors and Mayo Clinic database.

**Results:**

Summary of the demographic and pathologic features of 75 cases of thoracic PNST

<table>
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<th>Endobronchial (n = 6)</th>
<th>Benign PNSTs</th>
<th>Pleuroparenchymal (n = 15)</th>
<th>Mediastinal (n = 49)</th>
<th>MPNST (n = 5)</th>
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<td>Size (cm)&lt;comma&gt; mean (range)</td>
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</tbody>
</table>

**Take home message:** A wide variety of benign PNSTs can occur in the lung as endobronchial or parenchyma masses. MPNSTs can occur in the lung and mediastinum where they show aggressive behavior and should prompt consideration of NF1

Weissferdt et al. Primary mediastinal seminomas: a comprehensive immunohistochemical study with a focus on novel markers. Hum Path 2015;46:376-383

**Background:** Compared to testicular seminomas, little is known about the expression of novel IHC markers in mediastinal seminomas.

**Methods:** 32 cases of primary mediastinal seminomas were stained using representative whole sections with antibodies against: CK5/6, CAM5.2, OCT3/4, SALL4, GATA-3, SOX-2, SOX17, TCL1, glypican 3, melanoma associated antigen C2 (MAGEC2), and PAX8. % of positive tumor cells and intensity of staining were scored.

**Results:**

Table 2. Staining % for IHC markers in 32 mediastinal seminomas

<table>
<thead>
<tr>
<th>%</th>
<th>CK5/6</th>
<th>CAM5.2</th>
<th>OCT3/4</th>
<th>GATA-3</th>
<th>SOX2</th>
<th>SALL4</th>
<th>TCL1</th>
<th>Pax8</th>
<th>Glypican</th>
<th>MAGEC2</th>
<th>SOX17</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>0 (100%)</td>
<td>4 (12%)</td>
<td>3 (9%)</td>
<td>(100%)</td>
<td>3 (9%)</td>
<td>(97%)</td>
<td>(94%)</td>
<td>(100%)</td>
<td>4 (13%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Table 3. Staining intensity of IHC markers in 32 mediastinal seminomas

<table>
<thead>
<tr>
<th>Staining intensity</th>
<th>CK5/6</th>
<th>CAM5.2</th>
<th>OCT3/4</th>
<th>GATA-3</th>
<th>SOX2</th>
<th>SALL4</th>
<th>TCL1</th>
<th>Pax8</th>
<th>Glypican 3</th>
<th>MAGEC2</th>
<th>SOX17</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>32 (100%)</td>
<td>4 (13%)</td>
<td>3 (9%)</td>
<td>32 (100%)</td>
<td>32 (100%)</td>
<td>4 (9%)</td>
<td>31 (97%)</td>
<td>30 (94%)</td>
<td>32 (100%)</td>
<td>4 (13%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Weak</td>
<td>0</td>
<td>5 (16%)</td>
<td>9 (28%)</td>
<td>0</td>
<td>0</td>
<td>(13%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>8 (25%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>6 (19%)</td>
<td>(34%)</td>
<td>0</td>
<td>0</td>
<td>(53%)</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>18 (57%)</td>
<td>0</td>
</tr>
<tr>
<td>Strong</td>
<td>0</td>
<td>(53%)</td>
<td>9 (28%)</td>
<td>0</td>
<td>0</td>
<td>(25%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Take home message: Contrary to testicular seminomas, mediastinal seminomas are diffusely positive for CAM5.2 and commonly negative for TCL1.


Background: PD-L1 is involved in a pathway that suppresses immune control and its expression in small cell lung cancer (SCLC) has not been widely known. It is a retrospective study on the prevalence and prognostic roles of PD-L1 expression in SCLC.

Methods: IHC on 102 SCLC specimens with PD-L1 Ab (Abcam, Cambridge, UK) using BenchMark XT (Ventana) system. Tumors with >5% of tumor cells were scored as positive for PD-L1 expression. Survival analysis with Kaplan-Meier method.

Results: 73 of 102 SCLC cases (71.6%) showed PD-L1 expression, which was correlated with a limited disease stage. SCLC pts with PD-L1 positive tumors showed significant longer overall survival (OS) than those with PD-L1 negative tumors (median OS 16.3 vs. 7.3 mos, p<0.001). Multivariate analysis showed that a good performance status, LD stage, and expression of PD-L1 were significantly predictive of better OS, independently of other factors.

Discussion: PD-L1 expression in NSCLC is lower than SCLC in this study and conflicting results in the literature as to its relation to prognosis. It may be due to various Abs used in different studies and variable threshold for positivity, among others.

Take home message: Expression of PD-L1 is present >70% of SCLC and associated with a better prognosis.
**Background:** To examine the PD-L1 expression in a thymic epithelial tumor (TET) using tissue microarray (TMA)

**Methods:** TMA constructed from 69 TETs and 17 nonneoplastic thymic controls (including 9 paired nonneoplastic thymuses adjacent to tumor). Three 600 μm cores were selected from each case. Majority of the cases were from initial dx, except for 6 cases from recurrence in other sites as well as within thymic/mediastinal location. After scoring for PD-L1, HE sections were used to reclassify tumors according to 2004 WHO classification using the original sections; for mixed histology, most dominant type was adopted for classification. Clone 15 (rabbit mAb, 1:1,000, Sino biological, Beijing, China) with DAKO/EDTA/Tris was used in the staining. CK5/6 stain was used to aid in the localization of PD-L1 expression to epithelial cells or lymphocytes.

- PD-L1 stain scoring: 0=no staining, 1=equivocal/uninterpretable staining, 2=weak staining, 3=intermediate-strong staining, on the epithelial cells; PD-L1\textsuperscript{high} for score 3 in all three cores and the rest as PD-L1\textsuperscript{low} for analysis

- Tumor associated lymphocytes (TALs) were scored based on their % in the core: 1=minimal, 2=≤25%, 3=>25%

- Event-free survival (EFS) for those cases without metastases at initial dx measure from the date of dx to the date of recurrence or death. Overall survival (OS) was measured from the date of dx to the date of death. Adjustment variables included age, sex, Masaoka-Koga stage or WHO histology or resection status.

**Results:** TETs stain intensely and diffusely for PD-L1, with staining found mostly on epithelial cells and in a minority of TALs

- More intense PD-L1 staining associated with higher grade WHO histologies

- PD-L1\textsuperscript{high} TETs have a worse prognosis after adjusting for age and sex

- TALs are not independently prognostic and reflect WHO histology

**Take home message:** PD-L1 expression was seen in all TETs within the epithelial component but only in a minority in the lymphocytic component. TETs stained more intensely for PD-L1 than in controls and PD-L1\textsuperscript{high} TETs were associated with more aggressive histology and worse prognosis.

**Carbone et al.** Recent insights emerging from malignant mesothelioma genome sequencing. J Thorac Oncol 2015;10(3):409-411
Editorial for the following paper by Iacono et al. that was compared with another recently published paper by Guo G et al. *Whole exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A and CUL1 in malignant pleural mesothelioma*. Cancer Res 2015;72:264-9.


**Background:** One of the first landscape view of the somatic genomic alterations in MM.

**Methods:** A retrospective study on 123 FFPE tissue samples with clinical annotations using a commercial library kit (Ion AmpliSeq Cancer Hotspot Panel v.2, Life Technologies, Grand Island, NY) to investigate 50 genes plus two additional genes that are not included in this panel: BRCA-associated protein-1 (BAP-1) and neurofibromatosis-2 (NF2). The positive results were validated by Sanger sequencing. IHC for BAP-1 and NF2 was also performed.

**Results:** 20 of 52 “cancer genes” studied harbored variations in 25 of 123 (20%) of FFPE biopsies (including intronic, synonymous, nonsynonymous, and regulative mutations). These mutations were clustered in the two main pathways: p53/DNA repair (*TP53, SMACB1, and BAP1*) and phosphatidylinositol 3-kinase-AKT pathways (*PDGFRα, KIT, KDR, HRAS, PIK3A, STK11, and NF2*). The accumulation of genetic alterations correlated with shorter time to progressive disease and reduced overall survival. *BAP1* genetic variations were mainly located in exons 13 and 17, and *BAP1* nonsynonymous variations were significantly correlated with BAP1 protein nuclear localization.

**Take home message:** A complex mutational landscape mainly involving p53/DNA repair and phosphatidylinositol 3-kinase pathways is found in MM, some of which had a prognostic implication.


**Background:** Distinction between lung ADC and SqCC can be difficult. They quantify the inaccuracy by histopathologic exam in a cancer center between bx’s and resected specimens and evaluated the utility of a microRNA-based method.

**Methods:** RNA based study using FFPE tissue to measure MicroRNAs by TaqMan RT-PCR.

**Results:** 21% of 190 biopsies were failed or mistyped by routine histopathologic examination. Their microRNAs miR-21, miR-205 and miR-375 developed using 77 resected specimens for ADC and Sqcc typing offered the correct classification in 96% of 25 biopsies, 12 of which had been mistyped on histologic examination.

**Take home message:** I think the currently available IHC (TTF1, p40, CK5/6, DSG3, etc.) should be enough for this purpose and it is really hard to justify microRNA study for this purpose.
**Akaike et al.** Distinct clinicopathological features of NAB2-STAT6 fusion gene variants in solitary fibrous tumor with emphasis on the acquisition of highly malignant potential. Hum Path 2015;46:347-356

**Background:** The impact of NAB2-STAT6 fusion on biologic behavior and the mechanism of acquisition of malignant SFT are not well understood.

**Methods:** Variations of the NAB2-STAT6 fusion gene were studied in 40 cases of thoracic and extrathoracic SFTs together with the genetic alterations of TP53, PDGFRB, and TERT promoter and compared these genetic features with the clinicopathological features.

**Results:** STAT6 was positive in all 40 cases including CD34 negative cases and NAB2-STAT6 fusions were detected in all cases as well (n=18, NAB2 exon4-STAT6 exon 2; thoracic location and less aggressive; n=7 NAB2 exon6-STAT6 exon 16/18 aggressive phenotype). p53 IHC positivity was associated with a lower disease free survival rate (DFSR) and also with higher Ki67 index, higher mitotic rate (>4/HPF), and the presence of nuclear atypia/pleomorphism. Mutations in TP53 (n=2) and PDGFRA (n=3) were mutually exclusive. TERT promoter hot spot mutations (n=5) were associated with shorter DFSR and two dedifferentiated SFTs harbored both TP53 and TERT mutations.

**Take home message:**

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**Yatabe et al.** EGFR mutation testing practices within the Asia Pacific region. J Thorac Oncol 2015;10(3):438-445

**Background:** EGFR mutation testing is commonly done but the accurate data are lacking on the proportion of NSCLC patient tested in each country and the details of testing method. The primary objectives were 1. Determine the number of NSCLC pts who were tested for EGFR mutations at the surveyed sites and 2. to estimate the rate of EGFR mutation positivity in the tested smaples: overall, and by NSCLC histological subtype, sex, and smoking status. Secondary objectives were: 1. To estimate the
proportion of NSCLC pts who were tested in the participating countries: overall, and by NSCLC histological subtype, sex and smoking status, 2. to determine which EGFR mutation testing methods are most commonly used in the participating countries and the characteristics of smaples tested, and 3. To evaluate the source of the captured data and utilize this information to interpret the outcomes.

**Methods:** A retrospective database survey of records from NSCLC patients tested for EGFR mutations from Jan 1, 2011 to Jan 1, 2012 was done at participating sites in 11 countries across the Asia Pacific region. 40 of initial 71 shortlisted sites were selected in the study. Eligible sites had to answer online questionnaire.

**Results:** Of the 22,193 NSCLC pt records surveyed, 31.8% were tested for EGFR mutations. The rate of EGFR mutation positivity was 39.6% among the 10,687 cases tested. The majority of samples were bx and/or cytology smaples (71.4%). DNA sequencing was the most commonly used testing method for 40% and 32.5% of tissue and cytology samples, respectively. A pathology report was available only 60% of the sites and 47.5% were not members of a Quality Assurance Scheme.

**Take home message:** In 2011, EGFR mutation testing practices varied widely across Asia. The data provide a reference platform from which to improve the EGFR mutation testing.


**Background:** Patients with metastatic KRAS mutant lung cancers have been shown to have a shorter survival compared to those with KRAS wild-type cancers. Recent reports have suggested different clinical outcomes and distinct activated signaling pathways depending on KRAS mutation subtype. This study sought to investigate the impact of KRAS mutation subtype by analysis the data from 677 patients with KRAS mutant metastatic lung cancers

**Methods:** All patients with metastatic or recurrent lung cancers with KRAS mutations over a 6-year period (2005-11): association s among KRAS mutation type, clinical factors, and overall survival in univariate and multivariate analysis. Any significant findings were validated in an external multi-institution patient dataset.

**Results:** Table 4. Overall survival by Kras subgroup in original KRAS dataset
Take home message:  No apparent differences in outcome based on KRAS mutation subtype

Reviews/Essays


Weibel. On the tricks alveolar epithelial cells play to make a good lung. Am J Respir Crit Care Med 2015;191(5):504-513: A renowned Dr. Weibel’s fascinating essay on alveolar epithelial cells

Meiners et al. Hallmarks of the ageing lung. Eur Respir J 2015;45:807-827: Nine hallmarks of ageing have been defined as cell-autonomous and non-autonomous pathways involved in ageing: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, altered intercellular communication and stem cell exhaustion. The reviewed the involvement of each of these hallmarks in the pathogenesis of COPD, lung cancer, or IPF. They proposed an additional hallmark dysregulation of the ECM that acts as a crucial modifier of cell-autonomous changes and functions and as a key feature of COPE, lung cancer and IPF.


Kosmidis et al. The clinical spectrum of pulmonary aspergillosis. Thorax 2015;70:270-277: A detailed review on aspergillosis. They concluded that clinical syndromes caused by Aspergillus can be viewed as a continuous spectrum of disease whose manifestations are defined by the interaction between pathogen and host. One form of clinical disease may evolve into another over time depending on the degree of immune compromise of the host.

Iacono et al. Future options for ALK-positive non-small cell lung cancer. Lung Cancer 2015;87:211-219: With the introduction of second-generation ALK-TKI ceritinib, the treatment landscape of ALK-positive NSCLC evolves rapidly. They reviewed the current knowledge of ALK-positive advanced NSCLC and new development on combination regimens in the future.

Pelosi et al. Large cell carcinoma of the lung: A tumor in search of an author. A clinically oriented critical reappraisal. Lung Cancer 2015;87:226-231: Seven issues on LCC have been addressed by question and answer format: 1. LCC existence: To be or not to be-YES; 2. Are NSCLC-NOS dx in bx and cytology the same as LCC? YES from a practical point of view; 3. Is LCNEC part of LCC category?-YES; 4. How to classify non-neuroendocrine undifferentiated LCC? Exclude solid ADC, mets and sarcomatoid carcinoma, then proceed to immunoprofiling; 5. Is it possible to define diagnostic algorithms by IHC? YES and reduce the LCC category; Is the search for predictive markers useful in LCC category?-YES; 7. Is survival of LCC the same as that of differentially more refinable tumors?-NO
They concluded that it seems safer and wiser to accept that a minority of primary lung cancers completely devoid of signs of differentiation may elude any eventual classification.

**Byers et al. Small cell lung cancer: Where do we go from here? Cancer 2015;121:664-72** The authors review the current status of SCLC treatment, recent advances in current understanding of the underlying disease biology, and the opportunities to advance translational research and therapeutic approaches for patients with SCLC.

**Case report**

Robesova et al. Identification of atypical ATRN1 insertion to EML4-ALK fusion gene in NSCLC. Lung Cancer 2015;87:318-201 A report of previously unrecognized insertion of a gene to the well-known EML4-ALK fusion gene, which highlights the EML4-ALK heterogeneity. The patient was a 61 year old man and responded to crizotinib therapy.