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Articles for Discussion

Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Yoshida A et al. Modern Pathology 2017; 30: 797-809

Background

- Numerous epigenetic processes related to chromatin and DNA modifications are affected by somatic mutations.
- The family of adenosine triphosphate (ATP) dependent chromatin remodeling complexes can be subdivided into five different classes: SWI/SNF, ISWI, NuRD/Mi2/CHD, INO80, and SWR1.
- The switch/sucrose-non-fermenting (SWI/SNF) is a family of ATP dependent chromatin remodeling complexes that plays important roles in transcription, differentiation, and DNA repair.
- SWI/SNF complexes contain a single ATPase, either BRM (encoded by the SMARCA2 gene) or BRG1 (SMARCA4), and three main core subunits: BAF155 (SMARCC1), BAF170 (SMARCC2), and BAF47 (SMARCB1). The composition of SWI/SNF complexes is highly variable and depends on cellular and developmental contexts.
- Mutations are detected by loss of IHC expression.
- They are altered in many cancer types (20%, similar to frequency of TP53), and are probably the most frequently mutated epigenetic regulators.
- Malignant rhabdoid tumors (MRT) are characterized by the >95% presence of bi-allelic inactivating mutations of the SMARCB1 gene4 and IHC loss of SMARCB1 expression. A subset of SMARCB1-intact MRT harbors SMARCA4 mutations, with IHC loss of SMARCA4.
- >90% of epithelioid sarcomas lack SMARCB1 expression.
- An inactivating mutation of SMARCA4 (or rarely SMARCB1) was identified in >95% of small cell carcinomas of the ovary, hypercalcemic type.
- The SWI/SNF complex mutations can also occur in common carcinomas in older population.
- SMARCA4 mutation and/or loss of SMARCA4 IHC in lung cancers occurs in ~ 10% of poorly differentiated adenocarcinomas, wild type for EGFR and ALK, typically affect smoking men, and are associated with worse survival.
- In addition, SWI/SNF complex abnormality occurs in the process of carcinoma dedifferentiation, e.g, SMARCA4 or SMARCB1 deficiency occurs in 24–50% of dedifferentiated endometrial adenocarcinomas.
- Le Loarer et al.(28) described 19 patients with a high-grade thoracic neoplasm that harbored SMARCA4 inactivating mutation. In contrast to lung carcinomas with isolated SMARCA4 inactivation, these SMARCA4-deficient thoracic malignancies also showed co-deficiency of SMARCA2. These tumors often involved the mediastinum, sometimes the lung as well, occurred in relatively young patients and had aggressive behavior.
- Consistent clinicopathological findings and distinctive expression profile led to the proposal of a new entity, SMARCA4-deficient thoracic sarcomas (SMARCA4-DTS).
The diversity of composition of these complexes is shown. SWI/SNF complexes are composed of evolutionarily conserved core subunits (green) and variant subunits (yellow). The BRG1-associated factor (BAF; also known as SWI/SNF-A) and polybromo BRG1-associated factor (PBAF; also known as SWI/SNF-B) complexes constitute major subclasses. AT-rich interactive domain-containing protein 1A (ARID1A; also known as BAF250A and SMARCF1) and ARID1B (shown in blue) are unique to BAF complexes, whereas BAF200, BAF180 (also known as PBRM1) and bromodomain-containing 7 (BRD7) (shown in red) are unique to PBAF complexes. b | Mechanisms of remodelling are shown. The steps of remodelling include SWI/SNF binding, disruption of histone–DNA contacts, the creation of a loop of DNA that propagates around the nucleosome in a wave-like manner and the repositioning of DNA with respect to the nucleosome (sliding). Sliding may also lead to the ejection of an adjacent nucleosome. BRG1, BRM/SWI2-related gene 1 (also known as SMARCA4); BRM, brahma homologue (also known as SMARCA2). Wilson et al. Nature Reviews Cancer 2011 11, 481-49
SWI/SNF complexes are markedly under-represented at silent genes where nucleosomes are poorly positioned and are highly variable across individual cells of the same lineage (top of the figure). At active genes that are rich in SWI/SNF binding (bottom left of the figure) the transcription start site (indicated by an arrow) is flanked by precisely positioned nucleosomes, thus providing unobstructed access to a nucleosome-depleted region that contains transcription factor binding sites. SWI/SNF complexes also contribute to the dynamic silencing of targets that are required for lineage-specific differentiation and that facilitate the binding of repressors (bottom right of the figure). CDK1, cyclin-dependent kinase 1; RNA Pol II, RNA polymerase II. Wilson et al. Nature Reviews Cancer 2011 11, 481-492

Aim: In order to better characterize this emerging entity the authors undertook a clinicopathological and molecular analysis of archival cases and compared them with potentially related diseases.

Materials and methods

- Unclassifiable round cell or epithelioid-cell sarcomas retrieved from local pathology files
  - Tumors that had been originally diagnosed as epithelioid sarcomas despite the absence of SMARCB1 deficiency.
  - High-grade tumors that were originally suspected or diagnosed as undifferentiated carcinomas, that either affected the thoracic region or lacked clear information on the primary sites
- 42 tumors - SMARCA4 antibody.
- 12 tumors with significant thoracic involvement and complete loss or severe diffuse reduction of nuclear immunoreactivity of SMARCA4.
- For comparative purposes:
o 13 MRT, of which 11 lacked SMARCB1 expression and 2 were deficient for SMARCA4 expression
o 12 epithelioid sarcomas (all in adults), all of which lacked SMARCB1 expression
o 12 lung adenocarcinomas that were deficient for SMARCA4 immunoexpression

IHC: cytokeratin (AE1/AE3, 1:100; Dako, Glostrup, Denmark), SMARCB1 (25/BAF47, 1:100; BD Biosciences, Franklin Lakes, NJ, USA), SMARCA4 (EPNCIR111A, 1:200; Epitomics, Burlingame, CA, USA), SMARCA2 (HPA029981, 1:800; Sigma-Aldrich, St. Louis, MO, USA), CD34 (QBEnd10, 1:100; Dako), SALL4 (6E3, 1:1000; Abnova Corporation, Taipei, Taiwan), and SOX2 (AB5603, 1:1000; EMD Millipore, Billerica, MA, USA). p53 (DO-7, 1:100; Dako), TTF-1 (8G7G3/1, 1:100, Dako), and claudin-4 (3E2C1, 1:500, Zymed Laboratories, San Francisco, CA, USA)

Genetic Analysis: targeted NGS analysis in 5 cases using an original cancer gene panel, NCC oncopanel v4 designed using SureDesign (Agilent Technologies, Santa Clara, CA, USA) to capture all coding exons of 114 genes and reported translocated introns of 12 genes (Supplementary Table 4).

Statistical Analysis
Overall survival, from the date of the patient’s presentation to the facility where treatment was initiated, was determined using the Kaplan–Meier method.

Results

Clinical Findings (Table 1)

- M/W 11/1
- 27 - 82 years (median, 39 years).
- All patients were Japanese.
- 7/10 heavy (>20 pack × years) smoking exposure.
- 10/12 bilateral pulmonary emphysema, bullae, or both, including 2 patients who reported no smoking history.
- Size: 3.7-14 cm
- Primary tumor sites - thoracic wall, thoracic cavity, mediastinum, or the lung in 9 cases. 8 tumors involved the thoracic cavity at least focally, whereas 1 tumor (in case 6) involved the axillary soft tissue without involvement of the thoracic cavity. Case 12 presented with a mass involving the RUL and the mediastinum, and subsequently developed a large ovarian tumor in 4 months.
- In 3 cases determining the primary tumor site was problematic as they had a large lung or mediastinal mass but also abdominal/retroperitoneal or pelvic mass.
- Most patients presented with metastatic disease. The tumors were resected for palliative purposes in 2 patients, and the remaining 10 patients received biopsy only. Chemotherapy was administered to 6 patients.
- Median overall survival - 7 months

**Pathological Findings**

- Gross: available for 4 cases, - white or soft.
- Biopsies only - 8, both biopsies and autopsy specimens - 2, and resections - 2.
- Histologically, all similar - diffuse sheets of mildly dyscohesive large epithelioid cells (Figures 2a and b). Lightly eosinophilic cytoplasm with focal clearing in some cases, vesicular chromatin and 1–3 prominent nucleoli (Figures 2c and d). Rhabdoid cells (abundant eosinophilic cytoplasm, eccentric nuclei, perinuclear hyaline inclusions) were present in 6 cases. Two tumors contained focal spindled component (Figure 2e). Relatively monotonous with mostly mild nuclear pleomorphism.
- Mitoses 3–12/high power field. All tumors showed geographic necrosis.
- No differentiation in the form of glandular formation, papillary structure, keratinization, neuroendocrine morphology, or specific mesenchymal lineage.
- One exceptional finding noted in 1 case (case 11) was a prominent myxoid stroma in which tumor cells grew in a reticular manner (Figure 2f).
- The original pathological diagnoses were inconclusive in 9 cases -high-grade malignancy, with sarcomas or carcinomas being variably favored. Three tumors originally received definitive diagnoses of undifferentiated carcinoma, large-cell variant of Ewing sarcoma, and proximal-type epithelioid sarcoma.
Figure 2  SMARCA4-deficient thoracic sarcomas showed diffuse sheets of large epithelioid cells (a and b). The tumor cells were relatively monotonous with mild nuclear pleomorphism and harbored amphophilic or lightly eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli (c and d). Rhabdoid cells were focally present in 6 cases (d inset). Two tumors showed spindle cell component (e), and one case focally showed a prominent myxoid stroma with reticular growth (f).
- Complete lack (8 cases) or diffuse severe reduction (4 cases) of SMARCA4 expression.
- SMARCA2 expression was deficient in 11 cases.
- SMARCB1 was retained in all 9 cases tested.
- Cytokeratin (AE1/AE3), CD34, SOX2, and SALL4 were expressed in 6, 10, 10, and 10 cases, respectively.
- p53 expression was positive in 7 out of 10 cases tested, all of which exhibited diffuse strong staining in >90% of cells.
- Claudin-4 was negative in all 8 cases tested.
- Positive reactivity to CAM5.2 (1/1), CK7 (1/3), TTF-1 (1/10, focal).

**Molecular Findings**

5 cases, each of which harbored inactivating SMARCA4 mutations, including nonsense or frame-shift mutations. Additional gene aberrations were detected in TP53, NF1, KRAS, KEAP1, CDKN2A, ARID1A, EP300, CREBBP, and MYC among others (Table 2 and Supplementary Table 5).

**Clinicopathological Comparison with Potentially Related Entities (Table 3 and sup 1-3)**

- Most (11/13) MRT lost SMARCB1, while the remaining 2 were deficient in SMARCA4. Other immunoprofiles of MRT were similar to SMARCA4-DTS, in that many expressed CD34 (6/13), SOX2 (10/13), and SALL4 (12/13). In addition, similar to thoracic sarcomas, SMARCA2 expression was deficient in 6 out of 12 MRT successfully tested. The remaining 6 cases exhibited heterogeneous SMARCA2 staining, in which geographic foci of staining loss or reduction were interspersed among immunopositive area. p53 was overexpressed in none.
- **Epithelioid sarcomas** (n = 15) median age of 34 (range, 20–52 years). They occurred in the genital/inguinal region (6), extremity (5), trunk wall (3), and head and neck (1), and histologically classified as distal (7), proximal (5), or hybrid (3) types. Although distal-type

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### Table 2: Immunohistochemical and molecular results of SMARCA4-deficient thoracic sarcomas

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**Note:**

- Complete lack (8 cases) or diffuse severe reduction (4 cases) of SMARCA4 expression.
- SMARCA2 expression was deficient in 11 cases.
- SMARCB1 was retained in all 9 cases tested.
- Cytokeratin (AE1/AE3), CD34, SOX2, and SALL4 were expressed in 6, 10, 10, and 10 cases, respectively.
- p53 expression was positive in 7 out of 10 cases tested, all of which exhibited diffuse strong staining in >90% of cells.
- Claudin-4 was negative in all 8 cases tested.
- Positive reactivity to CAM5.2 (1/1), CK7 (1/3), TTF-1 (1/10, focal).
epithelioid sarcomas were morphologically distinctive due to granuloma-like arrangement, proximal-type morphology overlapped with that of SMARCA4-DTS. Co-expression of cytokeratin and CD34, 11/15 epithelioid sarcomas, all but 1 epithelioid sarcoma lacked expression of SOX2 and SALL4, and 14/15 epithelioid sarcomas retained SMARCA2 reactivity.

- **SMARCA4-lung carcinoma** – median age 55.5 years (range: 44–69 years). Most heavy smokers. All adenocarcinoma; sheets of more cohesive epithelial cells with only 1 tumor showing focal dyscohesive growth. Significant pleomorphism present in 7/12. Solid (7), acinar (1), solid and acinar (4). 4 showed concomitant SMARCA4-proficient better-differentiated element with a sharp border to SMARCA4-deficient growth. CK strong diffuse in all, TTF-1 focal in 6. SMARCA2 pos in 11/12. Claudin-4 positive in 12/12.

**Discussion:** Similar to Le Loarer et al.28 - validates the concept of SMARCA4-DTS but broader disease spectrum - abdominal diseases in 3 cases - strict exclusion of abdominal primary was impossible.

**Differential diagnosis**
- MRT- overlapping morphological and expression profiles but much younger population, associated with germ-line mutation of SMARCB1 or SMARCA4 in 33%, no SMARCA4 germ-line mutation has been identified in SMARCA4-DTS which have a complex genomic profile.
- In contrast to epithelioid sarcomas, none of the SMARCA4-DTS affected the extremities or genital regions. > 90% epithelioid sarcomas lack SMARCB1 expression and retain SMARCA4. Opposite immunoprofile to SMARCA4-DTS
- Germ-cell tumors: SALL4 expression in SMARCAA4-deficient thoracic sarcomas is often focal and they lack OCT3, CD30, and placental alkaline phosphatase expression
- NUT-midline carcinomas can co-express cytokeratin and CD34, but they may show squamous differentiation and express NUT and SMARCA4
- Ewing sarcomas: CD99 staining in SMARCA4-DTS was always focal and NKX2.2,50 was uniformly negative. Ewing sarcomas and Ewing-like sarcomas such as CIC-rearranged sarcomas retain SMARCA4 expression
- Mesothelioma rarely reported to lack SMARCA4 reactivity, but SMARCA2 expression retained
- Lymphomas, Thymic carcinomas
- SMARCA4-deficient lung carcinomas showed differential immunoprofile included staining pattern of cytokeratin (diffuse vs focal), TTF-1, CD34, SOX2, SALL4, SMARCA2, and claudin-4. Claudin-4 was positive in all carcinomas and negative in the sarcomas.

**Evidence for a distinct category of SMARCA4-DTS as compared with lung carcinomas**
- Phenotype appears distinct, similar to MRT, large size
- Molecular distinct- SMARCA2 deficient unlike lung carcinomas (in literature, <0.1% of lung carcinomas have co-deficient SMARCA4 and SMARCA2)
- Relatively young (but a wide age-range)

**Evidence for epithelial derivation of SMARCA4-DTS**
- consistent thoracic location
- epithelioid appearance
- focal cytokeratin expression in 50%
- many were diagnosed on small biopsies alone
• Many male heavy smokers with emphysema
• often genetically harbored C:G/A:T transversions similar to smoking-associated lung carcinomas
• KRAS is more commonly associated with epithelial tumors, and KEAP1 has been listed as one of the most significantly mutated gene in lung adenocarcinomas as compared to other tumor types; NF1, KRAS, and SMARCA4 are known to be more common in smoking-related adenocarcinomas
• analogy of SMARCA4-DTS to the undifferentiated component of dedifferentiated endometrial carcinomas - SMARCA4-deficient dedifferentiated endometrioid carcinomas are consistently co-deficient in SMARCA2 and may express SALL4 and/or CD34.

Attention is drawn to another paper which is an epub in June (and therefore not included formally in this journal club) - Sauter JL, Graham RP, Larsen BT, Jenkins SM, Roden AC, Boland JM. SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior. Mod Pathol. 2017 Jun 23.
  • Also mainly males, similar phenotype
  • Median age 59
  • All showed co-inactivation of SMARCA4 and SMARCA2 at the protein level.

Take home message:

• This paper provides further evidence that SMARCA4-DTS a distinct group of high-grade malignancy but has not definitively proven that they don't arise as dedifferentiation from lung carcinomas and further study is required
• Median age in this paper was 39, but 2 patients were in their 70s and one was 82 – therefore should be considered in all adult age groups
• Clinical picture may be predominated by abdominal metastases, but cannot definitively exclude that they didn't arise in the abdomen
• Careful clinicopathological assessment including an IHC panel (eg, SMARCA4, SMARCA2, cytokeratin, CD34, SALL4, TTF-1, and claudin-4) might solve the diagnostic dilemma for most instances including needle biopsy settings.
• Targeted therapies are being developed making it even more important to correctly identify these tumors, whether or not they arise from lung carcinomas
**Cicatricial Variant of Cryptogenic Organizing Pneumonia.** Yousem SA. Human Pathology 2017; 64: 76-82

**Background**

- Cryptogenic organizing pneumonia (COP, aka bronchiolitis obliterans with organizing pneumonia) is a subacute illness affecting middle-aged men and women that is sensitive to high-dose steroid therapy in an overwhelming majority of cases (>80%).
- Radiographically, COP is characterized by migratory ground glass opacities without honeycomb change, traction bronchiectasis, or other roentgenographic manifestations of irreversible lung injury.
- Since its initial description, the clinical and radiographic spectrum of disease has expanded. Fulminant and more chronic clinical courses of disease have emerged, and chest radiographs may display solitary nodules, multinodular infiltrates, and diffuse fine reticulonodular interstitial opacities.
- Histologically it is described as a patchy process with filling of the lumens of bronchioles and airspaces with loose fibromyxoid connective tissue, occasionally admixed with fibrin and accompanied by an alveolar septal mononuclear infiltrate. Irreversible scarring and honeycomb change are absent.
- Yousem observed cases of COP in which the loose fibromyxoid connective tissue of the organizing pneumonia displays progressive fibrosis with formation of intraluminal dense eosinophilic scar tissue without destruction of the underlying lung architecture. “Cicatricial forms of COP (CCOPs)”

**Aim:** To describe the clinical, radiological, and pathologic features of CCOP and compare these findings to historical data derived from other case series of classical COP.

**Materials and methods**

- The consultation files of the author were searched for cases coded as BOOP/COP with fibrosis in a 20-year period beginning in 1996.
- Criteria for a diagnosis of COP conformed to current definitions defined by international societies.
- 42 CCOP from 223 cases of COP were identified but 30 were eliminated because they had a known etiology/history of autoimmune disease, therefore 12 cases for study.
- In most instances, HRCT scans were unavailable for review. In these instances, data were extracted from the radiologic reports and focused largely on the quality of the infiltrates (nodules, reticulonodular/interstitial, ground glass/alveolar infiltrates), and the presence or absence of honeycomb change, irreversible architectural distortion and reticulation, traction bronchiectasis, or irreversible consolidative fibrosis.
- All available glass slides were reviewed (mean number, 8; median number, 6; range, 2-47). In all cases, elastic tissue stains were performed, as were silver stains for fungi and pneumocystis.
- Cases were excluded from the study: granulomas, honeycomb change with remodeled scarred lung parenchyma, and evidence of aspiration.

**Results**

**Clinical data:** Comparison to a historical group of 12 patients (10 of whom have been previously reported; Yousem et al Mod Pathol 1997;10:864-71)
M/W, 8/4 (COP 8/4)

Men age 56 y; range, 36-78 y (COP 68.2, 42-81)

Only 1 patient was asymptomatic. The remaining 11 had a variety of clinical complaints, predominantly shortness of breath (n = 10), dyspnea on exertion (n = 3), and dry cough (n = 2) of 1 to 14 weeks in duration (mean, 3.2 weeks; median, 6.1 weeks) prior to presentation to their pulmonologist. (COP: cough (8), dyspnea on exertion (5) fever (5) and chest pain (4), duration not given).

7 were current or past cigarette smokers (range, 10-40 pack-years; mean, 24); 3 were lifelong nonsmokers.

All treated with antibiotics prior to biopsy, and 2 were treated with low-dose steroid therapy.

Radiology:
- 10 - bilateral disease
- 2 - solitary nodules
- 8 - bilateral nodular infiltrates
- 2 - bilateral ground glass alveolar opacities
- 2 - interstitial reticulonodular infiltrates
- 4 - significant emphysematous change
- No honeycomb change, traction bronchiectasis, or cavitating nodules were present.

All treated with oral steroids for > 2 months (range, 2-168 months; mean, 77.6 months; median, 47 months).

11 had follow-up information:
5 (45%) - resolution of radiographic infiltrates and were without evidence of symptomatic or radiographic disease (2 of these were solitary nodules in which lesional tissue was excised).

4 (37%) - persistent radiographic infiltrates, without clinical symptoms

2 (18%) - progressive symptoms and radiographic infiltrates.

i.e. 55% had progressive or persistent nonprogressive radiographic disease despite steroid and, in 3 cases, methotrexate, azathioprine, and/or cyclophosphamide therapy

If solitary nodules are excluded, the percentage would rise to 67%

Clinical behavior did not correlate with the type of radiographic infiltrates (except excised solitary nodules) or any specific clinical complaint.

COP all alive and well without radiographic infiltrates after high-dose steroid therapy (average follow-up, 31 months; range, 4-83 months).

Pathology

- OLB in all 12 CCOP cases, with 2 or more lobes biopsied in 9 and a single lobe in 3 (2 of these 3 were solitary nodules)
- All multifocal centrilobular distribution of loose fibromyxoid polyps of granulation tissue within the lumen of small bronchioles and distal airspaces, associated with a mild lymphocytic bronchiolitis and patchy alveolar septal infiltrate of lymphocytes and plasma cells (Fig 1A & B)
- Airspace fibrinous exudates were absent
- 4- Scattered eosinophils
- 3- lymphoid aggregates adjacent to bronchovascular bundles or within interlobular septa.
- 7 - the reaction was superimposed on respiratory bronchiolitis with emphysematous change manifested as either small bullae or sclerotic alveolar septa, disconnected from the outer walls of small airways with such enlargement of pores of Kohn that club-shaped septa appeared to be floating in alveolar spaces

![Fig. 1 CCOP: A, Airspaces are filled with branching plugs of intraluminal/intra-airspace granulation tissue. At left, the fibromyxoid tissue is loose and edematous, whereas elsewhere, it appears more eosinophilic, lamellar, and dense (original magnification, hematoxylin and eosin [H&E], ×100). B, Elastic tissue stain of the same field as panel A shows the luminal/airspace branching connective tissue with an intact alveolar elastic skeleton. The stain also highlights the dense lamellar and loose myxoid quality of the plugs (VVG, ×100).](image)

- 12 - usually in the center of the fibroinflammatory mass, the organizing granulation tissue was densely collagenized and eosinophilic with loose fibromyxoid tissue replaced by dense lamellar intraluminal collagen ("tendinous") with elongated fibroblasts that tethered alveolar septa of the air sacs and alveolar ducts to the central luminal scar tissue (Fig. 2A and B).
• Intact septal elastica drawn into the central eosinophilic fibrotic tissue, resulting in distortion of but not destruction of architecture.
• Macrophages and occasional lymphocytes were entrapped in the center of the cicatrix.

Fig. 2  CCOP: A, The organizing pneumonia obscures the underlying lung architecture, and the fibromyxoid plugs have become more cellular, collagenized, and dense, with inflammatory cells concentrated into the center of the fibrous plugs (H&E, ×200). B, At high magnification of panel A, the intra-airspace scar tissue appears dense and collagenized (H&E, ×400).

• The centrilobular portion of the inflammatory mass appeared to be scarred whereas the periphery of the nodule displayed the more typical loose fibromyxoid buds of luminal and intra-airspace loose connective tissue of COP (Fig. 3A and B).

Fig. 3  CCOP: A, At low magnification, CCOP shows the same pattern of injury as traditional COP, but in this case, the luminal plugs are densely hyalinized and fibrotic, lacking the typical loose myxoid quality of “Masson bodies” (H&E, ×100). B, In the same field as panel A, elastic tissue stain highlights the intraluminal nature of the scar and also demonstrates the maturation to dense scar tissue at the edges of the connective tissue polyps (VVG, ×100).
Elastic stains showed intact interstitial elastic tissue in the center and the periphery of the fibroinflammatory nodule, without the reduplication or loss seen in scars associated with chronic interstitial pneumonias such as UIP (Fig. 4A and B).

Many cases did display some fragmentation of elastica due to coexistent emphysema.

Additional findings
- chronic fibrous pleuritis (n = 4)
- osseous metaplasia and calcification (n = 3)
- pulmonary apical cap (n = 1)
- dust macules (n = 3)
- bronchiolectasis (n = 1).

Discussion
- In COP the underlying lung architecture is preserved during the healing process and that, over time, the lung parenchyma returns, for the most part, to its normal morphology as do chest radiographs.
- A morphologic variant—CCOP—showed maturation to irreversible dense mature eosinophilic scar tissue within the lumens of airways and airspaces.
- CCOP more often multifocal reticulonodular or nodular disease (82%) compared to COP (17%)
- 10% - 20% of patients with COP have progressive disease, with some rare cases having a fulminant course that terminates in the adult respiratory distress syndrome/diffuse alveolar damage
- A poor outcome in COP has been tied clinically to patients with underlying immunologic disorders especially autoimmune disease, severe hypoxemia, prior tobacco use, and bronchoalveolar lavage demonstrating increased eosinophils and neutrophils
- An adverse outcome in COP has been noted to be related to reticulonodular/nodular disease but morphology of these unresponsive cases has not been well defined.
- This study focused on a specific histologic variant of COP where a compact cordlike eosinophilic fibrosis tethered adjoining walls of alveolar septa together and contracted the lung parenchyma
in an accordion-like fashion, whereas the periphery of the fibroinflammatory process retained some of the typical myxomatous polyps within the airspaces.

- Fibrin exudation was absent or scant
- elastic tissue stains showed retention of the normal elastic network
- CCOP tends to occur in lung parenchyma that has been previously damaged- 58% of cases showed significant emphysematous change
- Sporadic reports in the literature refer to a “fibrosing” variant of COP
  - acute/subacute exacerbations of an underlying chronic interstitial pneumonia such as UIP
  - a form of disease where the alveolar septal interstitium is expanded by fibrous tissue as one would observe in fibrotic forms of NSIP or late organizing stages of diffuse alveolar damage.
- CCOP described represents a different process in which the airspace fibromyxoid tissue normally resorbed or broken down by collagenases instead undergoes collagen cross-linking and maturation, forming a linear pattern of scar tissue in the airspaces.
- Morphologic differential diagnosis of CCOP
  - Acute fibrinous and organizing pneumonia is dominated by massive exudation of fibrin
  - Hypersensitivity pneumonitis may have a prominent organizing pneumonia component but usually has readily identifiable poorly formed granulomas.
  - OP acute/subacute exacerbations of chronic interstitial pneumonias like UIP and NSIP
  - other etiologies that may result in hyaline fibrosis in OP include autoimmune disease, aspiration, and bronchiectasis.
- Limitations
  - Consultation cases so the complete medical records not available
  - Images from HRCT scans were not available to study

Take home message:
- Interesting paper but am not convinced this is a separate entity – have we been missing this all these years?
- Are the images convincing?
- Incomplete medical records may have missed autoimmune disease.

Background

- For patients with early stage disease lung cancer, surgical resection remains the cornerstone of treatment.
- The prognosis and subsequent clinical management decisions (such as adjuvant chemoradiation) are largely based on pathologic TNM staging.
- For most resected lung cancers, the pathologic tumor T staging is predominantly determined by gross measurement of the tumor at the time of specimen grossing.
- 8th edition of the AJCC Cancer Staging Manual stratifies the T stage of lung cancers based on every increasing 1.0-cm increment, up to 5.0 cm, with an upper staging size threshold of 7.0 cm.
- Accurate measurements of tumor sizes are therefore of the upmost importance, so that patients are staged correctly.

Aim: To determine if measurement bias is present in lung adenocarcinoma resection specimens by comparing pathology sample measurements with radiologic CT measurements.
Materials and Methods

Study Material

- 607 surgically resected lung adenocarcinoma specimens at authors institution from January 2005 through March 2015.
- Preresection CT scans in tumors with a final pathologically measured size of 8.0 cm or less were available for 493 cases available for this study. This threshold was chosen as 8.0 cm is 1.0 cm greater than the largest T-stage cutoff of 7.0 cm, measurements above which would have no bearing on pathologic tumor staging
- Only CT images reconstructed in the transverse plane were used in this study.

Tumor Assessment

- Measurements were recorded in three dimensions after formalin inflation and fixation and serial sectioning of the surgical specimen.
- The greatest measured dimension was used for pathologic T staging
- All radiologic images were rereviewed by one radiology observer with lung tumor measurements performed using a click-and-drag digital line-caliper tool built into PACS.
- There were no statistically significant differences in the distribution of measurements or the proportion of measurements falling on the half or whole centimeter between the original radiologist reports and the radiologist re-review sizes

Statistical Analysis

- Nonparametric Wilcoxon signed-rank test was used to test whether the mean measurements were statistically different between pathology and radiology.
- To test the hypothesis of measurement bias, the data were then grouped for both pathologic and radiologic measurements into a subset that was measured as a whole- or half-centimeter increment (ie, all measurements where the last digit is 0 or 5, such as 0.5 cm, 1.0 cm, 1.5 cm, etc) vs all remaining measurements.
- The McNemar method (based on 2 × 2 contingency distribution tables for paired data) was used to evaluate the whole/half-centimeter proportion change between the pathology and radiology data.

Results

- The greatest tumor dimension measurements from pathologic and radiologic assessment were plotted with a bar graph in (Fig 1)
- The distribution of lung adenocarcinoma measurements shows an overrepresentation of cases that were measured at each increasing 0.5-cm increment (Fig 1A)
- This pattern is not observed in the radiologic measurements of the same tumor data set (Fig 1B).
- On average, pathologic measurements were 0.096 cm smaller than radiology measurements, (P < .001).
The data were then separated by pathologic measurement into those cases that were measured as a whole- or half-centimeter increment (ie, all measurements where the last digit is 0 or 5, such as 0.5 cm, 1.0 cm, and 1.5 cm) vs all remaining measurements.

- The total number of whole or half-centimeter measurements was 212 (43.0%) of 493 as measured by pathology compared with 100 (20.3%) of 493 as measured by radiology, \( P < .001 \).
- 167 (33.9%) of 493 cases were measured on the whole or half centimeter by pathology that were not measured on the whole or half centimeter by radiology (Fig 2).
- Conversely, 55 (11.2%) of 493 cases were measured on the whole or half centimeter by radiology that were not measured on the whole or half centimeter by pathology.

Figure 1: Pathologic (A) and computed tomography (B) measurements of 493 resected lung adenocarcinomas.

Figure 2: Infographic showing the distribution of radiologic vs gross pathologic measurements.
• To assess the generalizability of this observed pathologic measurement bias, tumor size
measurements were compiled from the SEER database for all registered lung cancer specimens
that fit the same study criteria.
• The same measurement bias exists across the large national SEER database (Fig 3A).
• The total number of whole- or half-centimeter measured lung cancer cases was 352,539 (59.6%) of
591,691.
• Expanding this assessment to all cancers regardless of primary site, 2,054,835 (57.1%) of
3,597,685 cancers were measured as whole- or half-centimeter sizes (Fig 3B).

Figure 3A Pathologic tumor size measurements from lung
cancer (A) and cancer of any type (B) as compiled from
the Surveillance, Epidemiology, and End Results program
Discussion

- Study shows a significant bias for pathologic measurements to be recorded to half-centimeter increments at the time of grossing.
- This is not an institution-specific phenomenon, as similar bias was illustrated in pathologic measurements of lung cancers and cancer of any type in the large national SEER database.
- For the in-house resected lung adenocarcinoma cases, 43.0% of pathology measurements fell on 0.5-cm increments, while the same cases as measured by radiology fell on 0.5-cm increments in only 20.3% of cases.
- If the measurements were randomly and evenly distributed, it would be expected that 20% (two of the 10 possible trailing digits being a “0” or “5”) of the measurements would be reported as a whole- or half-centimeter increment - the radiologic measurements are in keeping with this expected distribution.
- From a pathologic standpoint, lung adenocarcinomas can be difficult to measure grossly:
  - if the tumor border is not well defined, due to either an irregular infiltrative border or the presence of a subtle lepidic growth pattern at the periphery
  - once the specimen is sectioned, the third dimension (perpendicular to the plane of sectioning) can be difficult to re-create, which can be of clinical consequence if this is the largest tumor dimension.
  - The tendency to round to the nearest 0.5 cm could be a result of rushing during a busy service time
  - or simply that the 0.5-cm intervals on a ruler are easier to see and labeled numerically, causing our eyes to focus on these measurement anchor points.
- In contrast, CT measurements in the context of the radiologic-determined lesion borders are largely unbiased to any particular size measurement, with the radiologist using a click-and-drag digital measurement tool to draw a line through the long and short axes of the lesion and the computer program rendering the corresponding exact measurement.
- Although the pathologic measurements overall demonstrated relatively good agreement with the radiologic measurements of resected lung adenocarcinomas, the pathologic measurements were slightly smaller on average (0.096 cm, \( P < .001 \)). This observation has been made previously, possibly attributable to
  - formalin fixation shrinking pathology specimens
  - peritumoral inflammatory reactions causing a larger reading on radiology
  - atelectasis/collapse of tumors with a predominantly lepidic growth pattern.
- There is a trend for the 0.1-cm measurements immediately bordering any 0.5-cm intervals to be markedly lower than the next 0.1-cm measurements. For example, the number of cases measured at 0.9 cm and 1.1 cm is not only much lower than the number of cases at 1.0 cm but also lower than the cases measured at 0.8 cm and 1.2 cm, respectively. This suggests that in tumors where the measurements would fall close to a 0.5-cm increment, the grossing pathologist tends to round these cases to the closest 0.5-cm increment and not give a more accurate measurement.
- Any cases that are 0.1 cm over the closest 1.0-cm interval but are rounded down at the time of grossing are subsequently downgraded by pathologic T stage.
- For lung cancers close to key size cutoffs, especially 3.0 cm (cutoff between T1c and T2a) and 5.0 cm (cutoff between T2b and T3), incorrect tumor measurements could potentially result in undertreating these patients with adjuvant chemoradiation.
Of the 104 tumors in this data set that pathology measured as 1.0, 2.0, 3.0, 4.0, or 5.0 cm, the staging based on the corresponding radiologic measurements would result in a tumor upstage in 44 (42%) cases, downstage in six (6%) cases, and no tumor stage change in 54 (52%) cases. Therefore, pathologic measurements that are biased toward these whole-centimeter sizes can potentially lead to tumor stage changes.

Another noteworthy change in the 8th Ed AJCC Cancer Staging Manual is that for part-solid, nonmucinous lung adenocarcinomas, the size of the invasive component is the measurement that defines the T stage. Determining the exact size of the invasive component can be difficult when the tumor does not fit on a single slide, there are multiple foci of invasion, or there is ambiguity in grossly differentiating invasive from noninvasive patterns at the cutting bench. In these cases, it is recommended that the percentage of invasive areas be multiplied by the total tumor size to estimate the size of invasion. Therefore the overall gross tumor size as measured by pathology is still vital for accurate T staging.

To confirm that these observations are not institution specific but rather reflect a widely generalizable source of potential pathologic measurement bias, the large national SEER cancer database for pathologic recorded tumor size data for all tumors regardless of primary site with 57.1% of cases falling on whole- or half-centimeter increments.

A previous study has shown that this type of bias is present in small breast cancer specimens measured grossly but not when breast tumors are measured microscopically and a similar type of measurement bias has been seen in other forms of data collection, such as infant birth weight.

This highlights a general tendency to round numbers to major gradations when taking analog measurements of a continuous variable such as length.

**How to minimize this bias?**

- The simple recognition that this phenomenon exists may help operator take more care
- Introduction of options such as digital or mechanical calipers that give accurate measurements to a fraction of a millimeter

**Take home message:**

- A very interesting paper which draws attention to gross measurement bias by pathologists which has become more significant due to the increased stratification of tumor size for staging in the 8th Ed AJCC Cancer Staging Manual.
- Suggests that it is time that more accurate measuring tools be available such as calipers.
**Articles for Notation**

*Neoplastic*

**Pulmonary Sarcomatoid Carcinomas Commonly Harbor Either Potentially Targetable Genomic Alterations or High Tumor Mutational Burden as Observed by Comprehensive Genomic Profiling**


**ABSTRACT**

Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a high-grade NSCLC characterized by poor prognosis and resistance to chemotherapy. Development of targeted therapeutic strategies for PSC has been hampered because of limited and inconsistent molecular characterization.

Methods: Hybrid capture–based comprehensive genomic profiling was performed on DNA from formalin-fixed paraffin-embedded sections of 15,867 NSCLCs, including 125 PSCs (0.8%). Tumor mutational burden (TMB) was calculated from 1.11 megabases (Mb) of sequenced DNA.

Results: The median age of the patients with PSC was 67 years (range 32–87), 58% were male, and 78% had stage IV disease. Tumor protein p53 gene (TP53) genomic alterations (GAs) were identified in 74% of cases, which had genomics distinct from TP53 wild-type cases, and 62% featured a GA in KRAS (34%) or one of seven genes currently recommended for testing in the National Comprehensive Cancer Network NSCLC guidelines, including the following: hepatocyte growth factor receptor gene (MET) (13.6%), EGFR (8.8%), BRAF (7.2%), erb-b2 receptor tyrosine kinase 2 gene (HER2) (1.6%), and ret proto-oncogene (RET) (0.8%). MET exon 14 alterations were enriched in PSC (12%) compared with non-PSC NSCLCs (w3%) (p < 0.0001) and were more prevalent in PSC cases with an adenocarcinoma component. The fraction of PSC with a high TMB (>20 mutations per Mb) was notably higher than in non-PSC NSCLC (20% versus 14%, p ¼ 0.056). Of nine patients with PSC treated with targeted or immunotherapies, three had partial responses and three had stable disease.

Conclusion: Potentially targetable GAs in National Comprehensive Cancer Network NSCLC genes (30%) or intermediate or high TMB (43%,>10 mutations per Mb) were identified in most of the PSC cases. Thus, the use of comprehensive genomic profiling in clinical care may provide important treatment options for a historically poorly characterized and difficult to treat disease.

**Towards a Molecular Classification of Pulmonary Sarcomatoid Carcinomas (Editorial).** Mansfield AS et al.  Journal of Thoracic Oncology 2017; 12: 910-912

Take home point: Pulmonary sarcomatoid carcinomas are <1% of lung cancers, and are a very heterogenous group, they have a very poor prognosis, metastasizing early and have a poor response to systemic therapy. Shrock et al. found that 30% of their cases had potentially targetable genomic alterations giving rise to hope that these patients may benefit from targeted or immune therapy.

Introduction: Molecular subtyping of lung adenocarcinoma (AD) and lung squamous cell carcinoma (SCC) reveal biologically diverse tumors that vary in their genomic and clinical attributes.

Methods: Published immune cell signatures and several lung AD and SCC gene expression data sets, including The Cancer Genome Atlas, were used to examine immune response in relation to AD and SCC expression subtypes. Expression of immune cell populations and other immune related genes, including CD274 molecule gene (CD274) (programmed death ligand 1), was investigated in the tumor microenvironment relative to the expression subtypes of the AD (terminal respiratory unit, proximal proliferative, and proximal inflammatory) and SCC (primitive, classical, secretory, and basal) subtypes.

Results: Lung AD and SCC expression subtypes demonstrated significant differences in tumor immune landscape. The proximal proliferative subtype of AD demonstrated low immune cell expression among ADs whereas the secretory subtype showed elevated immune cell expression among SCCs. Tumor expression subtype was a better predictor of immune cell expression than CD274 (programmed death ligand 1) in SCC tumors but was a comparable predictor in AD tumors. Nonsilent mutation burden was not correlated with immune cell expression across subtypes; however, major histocompatibility complex class II gene expression was highly correlated with immune cell expression. Increased immune and major histocompatibility complex II gene expression was associated with improved survival in the terminal respiratory unit and proximal inflammatory subtypes of AD and in the primitive subtype of SCC.

Conclusions: Molecular expression subtypes of lung AD and SCC demonstrate key and reproducible differences in immune host response. Evaluation of tumor expression subtypes as potential biomarkers for immunotherapy should be investigated.

Immune Signatures of Non-Small Cell Lung Cancer (Editorial). Green, S. Immune Signatures of NSCLC 2017; 915

Take home point: Immunotherapy to treat NSCLC is an exciting recent development. Predictive biomarkers to identify patients that will have a long term response to these drugs are needed. As in breast cancer, the use of gene expression to define tumor subtypes in NSCLC has identified reproducible subtypes. Faruki et al. used multiple publicly available data sets of adenoca and SCC as well as adjacent non-tumor lung tissue, and investigated immune differences in these subtypes using 24 immune cell gene signatures. The databases are weighted with early stage lung cancers, and more later stage cancers need to be collected for study. Methodology complex and over my head but it is an interesting approach and did identify different immune signatures in the different tumors, so it is a start in the right direction.

Abstract: For lung squamous cell carcinomas, there are no histologic findings that have been universally accepted as prognostic factors. Tumor budding and nuclear grade have been recognized as prognostic factors in other carcinomas. In this study, we investigated whether pathologic findings could determine clinical outcome in Japanese patients with lung squamous cell carcinomas. Tumor slides from surgically resected lung squamous cell carcinomas (1999 to 2012) were reviewed (n=216). Tumors were evaluated for histologic subtypes, differentiation, tumor budding, nuclear diameter, and mitosis. Recurrence-free survival (RFS) and overall survival (OS) were analyzed using the log-rank test and the Cox proportional hazards model. Tumor budding and large nuclei were independent prognostic factors of a worse RFS (P<0.001 and P=0.002, respectively) and a worse OS (P<0.001 and P=0.038, respectively) on multivariate analysis after adjustment for pathologic stage and lymphatic invasion. However, histologic subtypes, differentiation, and mitotic count did not correlate with prognosis. A grading system combining tumor budding and nuclear diameter was an independent prognostic factors of a worse RFS (grade 2 vs. 1, hazard ratio [HR]=2.91; P<0.001, and grade 3 vs. 1, HR=7.60, P=0.002) and a worse OS (grade 2 vs. 1, HR=2.15; P=0.014, and grade 3 vs. 1, HR=4.54, P<0.001). We found that a grading system combining tumor budding and nuclear diameter was a significant prognostic factor among Japanese patients with resected lung squamous cell carcinoma.

Take home point: These authors have done several studies along these lines. There are many complex technical factors still to be worked out before this is ready for prime time.

PD-L1 Expression in Neuroendocrine Tumors of the Lung. Tsuruoka K et al. Lung Cancer 2017; 108: 115-120

Background: Various tumors express programmed cell death ligand 1 (PD-L1), an immune checkpoint ligand, the expression of which correlates with certain effects of anti-programmed cell death 1 (PD-1)/PD-L1 drugs. The aim of this study was to assess the frequency of PD-L1 expression in each of the types of neuroendocrine tumors of the lung.

Methods: The subjects enrolled in this study were patients who had been diagnosed with neuroendocrine tumors of the lung and had been treated at the National Cancer Center Hospital (Tokyo, Japan) between1982 and 2010. We performed immunohistochemical analysis on a tissue microarray (TMA) of the surgical specimens using the validated PD-L1 antibody clone, E1L3N. Tumor PD-L1 expression scores were calculated semiquantitatively (staining intensity [0–3] × stained area [0–100%]). A score of 1 was used as a cut-off to determine the presence or absence of PD-L1 expression.

Results: Among the 227 patients included in this study, the patient demographics were as follows: median age (range), 65 years (19–84); sex (male/female), 168/59; pStage (IA, IB, IIA, IIB, IIIA, IIIB, IV): 79, 36,25, 29, 47, 6, 5, respectively; and histology was typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), small cell lung cancer (SCLC): 46, 6, 106, 69, respectively. The numbers (proportions) of PD-L1-expression tumors were as follows: TC/AC/LCNEC/SCLC, 0/0/11 (10.4%)/4(5.8%).

Conclusions: PD-L1 expression was apparent in 10.4% of LCNEC and 5.8% of SCLC tumors, and was not observed in carcinoid tumors.
Take home point: This is the first report of PDL-1 expression in LCNEC tumors (~10%) and carcinoid (0%). Used a score of 0-300 with a score of 1 as the cut off for positivity. Unknown what is the clinically useful score to use as no clinical studies have been done.

**Peripheral-type small cell lung cancer is associated with better survival and higher frequency of interstitial lung disease.** Kanaji N et al. Lung Cancer 2017; 108: 126-133

Objectives: Small cell lung cancer (SCLC) can be subgrouped into central and peripheral types according to the location of the primary lesion. However, the clinical differences between these two types remain unclear. This study compared their clinical features.

Materials and methods: Data on 231 patients with pathologically diagnosed SCLC were retrospectively subgrouped into central or peripheral types. Progression-free survival (PFS), overall survival (OS), treatments, responses to first-line therapy, and frequency of interstitial lung disease (ILD) were compared between the two groups.

Results: Of the 231 patients, 101 (44%) had central-type and 130 (56%) had peripheral-type SCLC. Peripheral-type SCLC was associated with a better performance status, higher frequency of ILD, and higher rate of limited disease stage. Patients with peripheral-type SCLC had a significantly longer OS than did those with central-type SCLC (median, 502 vs 370 days, respectively; p = 0.0186). Tumor location was not associated with PFS. PFS was poorer in patients with than without ILD (median, 143 vs 213 days, respectively; p = 0.0038), as was OS (median, 245 vs 545 days, respectively; p = 0.0014). Among patients without ILD, OS was longer in those with peripheral- than central-type tumors (median, 662 vs 421 days, respectively; p = 0.0074). Surgical resection was more often chosen for peripheral-type tumors, and this was one reason for the prolonged survival. There was no difference in the response to chemotherapy and/or radiotherapy between central- and peripheral-type SCLC. Multivariate analysis by a Cox proportional hazards model showed that male sex, a poor performance status, extensive disease, the presence of ILD, an elevated serum neuron-specific enolase concentration, and central-type SCLC were poor prognostic factors for OS.

Conclusion: Peripheral type SCLC is associated with a better OS and a higher frequency of ILD than its central-type SCLC. The presence of ILD is a poor prognostic factor for both PFS and OS.

**Take home point:** Contrary to older reports, peripheral type SCLC is now more frequent than central type. In addition, 5% of SCLC patients were never-smokers. The peripheral type is often present within areas of ILD. Although OS is higher in peripheral type, presence of ILD is a poor prognostic factor and is commoner in peripheral type. It is still not clear if peripheral type are detected earlier or are just less aggressive.

**Clinicopathological, immunohistochemical, and mutational analyses of pulmonary enteric adenocarcinoma: usefulness of SATB2 and β-catenin immunostaining for differentiation from metastatic colorectal carcinoma.** Matsushima J et al. Human Pathology 2017; 64: 179-185

Summary Pulmonary enteric adenocarcinoma (PEA) is a rare variant of pulmonary adenocarcinoma; it is sometimes difficult to discriminate between PEA and metastatic colorectal carcinoma (MCRC) because
of their morphological and immunohistochemical resemblance. Here, we conducted clinicopathological, immunohistochemical, and mutational analyses of PEA with special focus on its differentiation from MCRC. We comparatively analyzed 8 surgically resected PEA tumors (7 patients) and 20 cases of MCRC. Patients were aged 43-77 years (average age, 64.1 years); 5 of 7 patients were men. Tumor sizes ranged from 1.5 to 11.5 cm (average size, 4.8 cm). The follow-up period was 1-65 months; 4 patients are alive without recurrence, 2 are alive with recurrence, and 1 patient died of idiopathic pulmonary fibrosis. Six of the tumors were pure PEA; one PEA tumor had a small mucinous adenocarcinoma component; another had a squamous cell carcinoma component. Immunohistochemically, the positive rates of PEA for each antibody were as follows: CK7, 88% (7/8); CK20, 88% (7/8); TTF-1, 13% (1/8); β-catenin, 0% (0/8, strong nuclear expression); and SATB2, 13% (1/8). The positive rates of MCRC for these antibodies were 10%, 95%, 5%, 55%, and 100%, respectively. Genetic analysis of KRAS, EGFR, and BRAF showed the G12V mutation.

Take home point: Differentiating pulmonary enteric adenocarcinoma from metastatic colorectal carcinoma can be difficult due to the PEA having identical IHC patterns to colorectal cancer in some cases with regard to CK7 (rarely, negative), 20, CDX2 (63-100% positive) and TTF-1 (low % are positive). PEA has a significantly lower nuclear beta-catenin positivity than colorectal cancer and only 1/8 were positive for SATB2 compared to 100% of colorectal. A relatively small study but appears that beta-catenin and more likely SATB2 are useful markers in differentiation.

**Prognostic impact of TTF-1 expression in patients with stage IV lung adenocarcinomas.** Schilsky JB et al. Lung Cancer 2017; 108: 205-211

Objectives: Thyroid transcription factor 1 (TTF-1) is routinely tested in the diagnostic evaluation of suspected lung cancers, is commonly expressed by lung adenocarcinomas, and may modulate lung cancer biology. We examined the role of TTF-1 as a predictive and prognostic marker in patients with advanced lung adenocarcinomas.

Materials and methods: We analyzed clinical, pathologic, and molecular features, treatments received, and overall survival obtained from the medical records of 479 consecutive patients at a single site with stage IV lung adenocarcinomas and evaluable TTF-1 expression. TTF-1 expression was determined by immunohistochemistry using antibody 8G7G3/1.

Results and conclusion: TTF-1 expression was evaluable in 479 (75%) of all patients reviewed, and was positive in 383 (80%, 95% CI 76–83%). Clinicopathologic features were similar between TTF-1 positive and TTF-1 negative tumors, except EGFR mutations were more common in TTF-1 positive cases (24% vs 6%, p < 0.001). In univariate analysis, overall survival was significantly longer in patients with TTF-1 positive versus TTF-1 negative tumors (18 months vs 9 months, p < 0.0001). In multivariate analysis, TTF-1 positivity remained associated with better overall survival (HR = 0.38, p < 0.0001), exceeding the prognostic impact of Karnofsky performance status ≥ 80% (HR 0.62, p = 0.0003) and receipt of first-line combination chemotherapy or targeted therapy (HR relative to first-line single agent chemotherapy 0.59, p = 0.05 and 0.51, p = 0.05 respectively). Both patients with TTF-1 positive and TTF-1 negative cancers had longer durations of initial therapy when treated with pemetrexed-based chemotherapy. In patients with advanced lung adenocarcinomas, TTF-1 expression is associated with better survival but is not predictive of distinct benefit from pemetrexed-based chemotherapy.
Take home point: Confirmation of better survival of TTF-1 (clone 8G7G3/1 Dako) positive lung adenocarcinomas first described in small studies.


Objectives: Pleural invasion has been recognized as an important negative prognostic factor in non-small cell lung cancer (NSCLC), and therefore, accurate evaluation is required. However, when the visceral pleura adheres to the parietal pleura around a tumor and parietal pleural structures are destroyed and unrecognizable as a result of inflammation, it is often difficult to accurately evaluate pleural invasion, and classification of the T stage is unclear. To aid in categorization, we defined this status as pl1-3 and investigated the prognostic impact of the pl1-3 status on NSCLC.

Materials and methods: We retrospectively examined the clinicopathological characteristics and prognoses of 929 NSCLC patients who underwent curative surgical resection. The pl1-3 status was defined as invasion beyond the elastic layer of the visceral pleura (pl1 or higher) but showing unclear parietal pleural invasion. We compared the prognoses of pl1-3 status NSCLC patients with that of patients with other pleural invasion statuses.

Results: Thirty-one patients (3%) had a pl1-3 status. The 5-year overall survival rate for pl1-3 patients was 58.9%, and the prognosis was significantly worse than pl1 (p = 0.04). In pN0 cohort, pl1-3 disease had a significantly worse prognosis than pl1 and pl2 diseases (p = 0.01 and 0.04, respectively) and a similar prognosis to pl3 disease. Furthermore, similar relationships were also observed after adjusting for other prognostic factors in multivariate analysis. Among the pl1-3 and pN0 patients, 11 (46%) developed recurrences (9 patients had distant metastasis, one had local recurrence, and one had both). Although the proportion of pl1-3 patients who underwent adjuvant therapy was similar to that of T3 patients, more individuals received oral tegafur-uracil treatment than intravenous chemotherapy.

Conclusion: These results indicate that pl1-3 patients can be managed in the same manner as patients with T3 and pl3 disease. These results may be informative for treatment decisions during postoperative chemotherapy.

Take home point: Nice paper which convincingly argues that patients in whom involvement of parietal pleura cannot be excluded due to firm adherence and destruction should be treated as if they were pl3.


Abstract Primary bronchopulmonary mucoepidermoid carcinoma (BPMEC) is a rare tumor. The fusion protein MECT1-MAML2 has been implicated as a causative genetic event in salivary and BPMECs. Several studies have shown the impact of MECT1-MAML2 on the diagnosis and prognosis of salivary gland mucoepidermoid carcinoma; however, few studies have been published regarding MECT1-MAML2 in the context of primary BPMEC. We describe the clinicopathologic, genetic, and outcome data of 16
patients with BPMEC. Clinicopathologic features were recorded from the electronic medical records. All tumors were reviewed by two expert pulmonary pathologists and graded according to previously established criteria. The presence of MECT1-MAML2 was evaluated with reverse transcription polymerase chain reaction using RNA extracted from formalin-fixed paraffin-embedded tumor tissue. Patients included 9 women and 7 men with a median age of 50 years (range, 7 to 82 years). Tumors exhibited low (n = 14, 88%), and high (n = 2, 12%) grade histologic features. Eight of nine tested tumors (89%) were positive for MECT1-MAML2. The median follow-up time was 40.8 months (range, 1.8–120). Median overall survival for patients with high-grade tumors was 12 months, which was significantly (p = 0.002) shorter than that for patients with low-grade tumors (survival undefined). We also provide a comprehensive review of literature of cases of primary bronchopulmonary mucoepidermoid carcinoma and summarize our findings in this context. MECT1-MAML2 fusion transcript is a driver genetic event in the pathogenesis of primary BPMEC. Histologic grade continues to play a pivotal role in the survival of patients with primary bronchopulmonary mucoepidermoid carcinoma.

**Take home point:** Good review of this rare tumor in the lung which nevertheless should be considered in small biopsies. 88% of low-grade (not high grade, unlike previous studies) primary bronchopulmonary mucoepidermoid carcinomas have MAML2 gene rearrangement and can be used diagnostically.


**First case of double ROS1- and AL-rearranged NSCLC.**


Background: Among patients with non–small-cell lung cancer (NSCLC), data on intratumor heterogeneity and cancer genome evolution have been limited to small retrospective cohorts. We wanted to prospectively investigate intratumor heterogeneity in relation to clinical outcome and to determine the clonal nature of driver events and evolutionary processes in early-stage NSCLC.

Methods: In this prospective cohort study, we performed multiregion whole-exome sequencing on 100 early-stage NSCLC tumors that had been resected before systemic therapy. We sequenced and analyzed 327 tumor regions to define evolutionary histories, obtain a census of clonal and subclonal events, and assess the relationship between intratumor heterogeneity and recurrence-free survival.

Results: We observed widespread intratumor heterogeneity for both somatic copy-number alterations and mutations. Driver mutations in *EGFR, MET, BRAF*, and *TP53* were almost always clonal. However, heterogeneous driver alterations that occurred later in evolution were found in more than 75% of the tumors and were common in *PIK3CA* and *NF1* and in genes that are involved in chromatin modification and DNA damage response and repair. Genome doubling and ongoing dynamic chromosomal instability were associated with intratumor heterogeneity and resulted in parallel evolution of driver somatic copy-number alterations, including amplifications in *CDK4, FOXA1*, and *BCL11A*. Elevated copy-number heterogeneity was associated with an increased risk of recurrence or death (hazard ratio, 4.9; P = 4.4×10−4), which remained significant in multivariate analysis.
Conclusions: Intratumor heterogeneity mediated through chromosome instability was associated with an increased risk of recurrence or death, a finding that supports the potential value of chromosome instability as a prognostic predictor.

Take home point: This is data from the first 100 samples of an ongoing multicenter study in which tumors from patients with NSCLC undergo high-depth, multiregion whole-exome sequencing; “Tracking NSCLC evolution through therapy, TRACERx”. The better we understand the processes at play in NSCLC, such as significant chromosome instability in NSCLC, the better we will be able to treat patients.


Context.—Immune checkpoint pathways, including programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) signaling pathway, which are important in mediating self-tolerance and controlling self-damage, can sometimes be manipulated by cancer cells to evade immune surveillance. Recent clinical trials further demonstrate the efficacy of PD-1/PD-L1–targeted therapy in various cancers and reveal a new era of cancer immunotherapy.

Objective.—To review the mechanism of the PD-1/PD-L1 signaling pathway, the regulation of this pathway, PD-1/PD-L1 as a predictive and/or prognostic marker in various cancers, and strategies of measuring PD-L1 expression.

Data Sources.—Representative medical literature regarding PD-L1 expression in various cancers, including the preliminary results of the Blue Proposal, which compares different immunohistochemical stains for PD-L1 reported in the recent American Association of Cancer Research (AACR) Annual Meeting (April 16–20, 2016).

Conclusion.—Either PD-1/PD-L1–targeted therapy alone or in combination with other treatment modalities provides benefit for patients with advanced cancers. Because of the complexity of cancer immunity, we still do not have a reliable biomarker to predict the response of PD-1/PD-L1–targeted therapy. Future studies, including methods beyond immunohistochemical stains, are needed to develop reliable biomarker/biomarkers for pathology laboratories to aid in selecting patients who will benefit most from PD-1/PD-L1–targeted therapy. A good review of all things PDL1 and PD1

Aims: The lung lesion [immunoglobulin (Ig)G4-L] of IgG4-related disease (IgG4-RD) is a condition that occurs together with IgG4-RD and often mimics the lung lesion [idiopathic multicentric Castleman’s disease (iMCD-L)] of idiopathic multicentric Castleman’s disease (iMCD). Because no clinical and pathological studies had previously compared features of these diseases, we undertook this comparison with clinical and histological data.

Methods and results: Nine patients had IgG4-L (high levels of serum IgG4 and of IgG4+ cells in lung specimens; typical extrapulmonary manifestations). Fifteen patients had iMCD-L (polyclonal hyperimmunoglobulinaemia, elevated serum interleukin-6 levels and polylymphadenopathy with typical lymphadenopathic lesions). Mean values for age, serum haemoglobin levels and IgG4/IgG ratios were higher in the IgG4-L group and C-reactive protein levels were higher in the iMCD-L group. All IgG4-RD lung lesions showed myxomatous granulation-like fibrosis (active fibrosis), with infiltration of lymphoplasmacytes and scattered eosinophils within the perilymphatic stromal area, such as interlobular septa and pleura with obstructive vasculitis. All 15 lung lesions of iMCD, however, had marked accumulation of polyclonal lymphoplasmacytes in lesions with lymphoid follicles and dense fibrosis, mainly in the alveolar area adjacent to interlobular septa and pleura without obstructive vasculitis.

Conclusions: Although both lesions had lymphoplasmacytic infiltration, lung lesions of IgG4-RD were characterized by active fibrosis with eosinophilic infiltration within the perilymphatic stromal area with obstructive vasculitis, whereas lung lesions of iMCD had lymphoplasmacyte proliferating lesions mainly in the alveolar area adjacent to the perilymphatic stromal area. These clinicopathological features may help to differentiate the two diseases.

Take home point: Not impressed by the utility of this study in differentiating these two conditions. There is some fanciful language used: “fibroblasts, compared with the wandering lymphoid cells, do not migrate easily, and thus IgG4 lesion would form mainly in the perilymphatic stroma area itself as active fibroblast proliferating lesions” which don’t make sense.

Restrictive allograft syndrome and idiopathic pleuroparenchymal fibroelastosis: do they really have the same histology? Montero MA et al. Histopathology 2017; 70: 1107-1113.

Aims: Restrictive allograft syndrome (RAS) and idiopathic pleuroparenchymal fibroelastosis (IPPFE) are two different diseases reported to share the same histology. RAS relates to chronic allograft dysfunction in lung transplantation, with IPPFE being a rare condition in native lungs. Our aim is to compare their histologies alongside biopsies of usual interstitial pneumonia (UIP), to determine if there are differences that might help to elucidate the pathogenesis.

Methods and results: We selected four postmortem allograft lungs from patients who developed a clear clinical RAS pattern, five biopsies diagnosed as IPPFE, five UIP biopsies and five sections of normal lung. Histopathological features were described without knowledge of clinical and radiological features. Both RAS allografts and IPPFE biopsies showed intra-alveolar fibrosis and elastosis (IAFE), but RAS allografts also showed concomitant obliteratorive bronchiolitis, vascular lymphoplasmacytic inflammation within
fibrointimal thickening, less fibroblastic foci (FF) at the advancing edge of the fibrosis (one against 14.4 FF in 2 mm²) and a slight reduction of the capillary network compared to UIP (P = 0.07) and controls (P = 0.06). The main differences seen in UIP were the lack of IAFE and the presence of honeycomb change.

Conclusions: RAS and PPFE histopathology both show IAFE, but display various differences, particularly in their vascular morphology that may allow further understanding of pathogenesis.

Take home point: Interesting paper but doubt that the differences they highlight will be useful to pathologists in differentiating these cases unless they have a good history.

The asbestos fibre burden in human lungs: new insights into the chrysotile debate


Abstract. The traceability of asbestos fibres in human lungs is a matter of discussion especially for chrysotile. This issue is of high significance for differential diagnosis, risk assessment and occupational compensation. At present no intra-individual longitudinal information is available. This study addresses the question whether the asbestos fibre burden in human lungs decreases with time after exposure cessation. The database of the German Mesothelioma Register was screened for patients with asbestos body counts of at least 500 fibres per gram of wet lung, which had been analysed twice from different tissue excisions at minimum intervals of 4 years. Twelve datasets with individual longitudinal information were discovered with a median interval of about 8 years (range 4–21 years). Both examinations were performed after exposure cessation (median: surgery, 9.5 years; autopsy, 22 years). Pulmonary asbestos fibre burden was stable between both examinations (median 1623/4269 asbestos bodies per gram wet lung). Electron microscopy demonstrated a preponderance of chrysotile (median 80%). This study is the first to present longitudinal intra-individual data about the asbestos fibre burden in living human lungs. The high biopersistence of amphiboles, but also of chrysotile, offers mechanistic explanations for fibre toxicity, especially the long latency period of asbestos-related diseases.


Take home point: Despite only 12 subjects examined, very important paper which illustrates that chrysotile asbestos is not removed rapidly from the lung but persists; this type of asbestos is not banned in several countries and represents a health hazard.


Acute respiratory distress syndrome (ARDS) is a major clinical problem with high morbidity and mortality. Diffuse alveolar damage (DAD) is considered the histological hallmark for the acute phase of ARDS. DAD is characterized by an acute phase with edema, hyaline membranes, and inflammation, followed by an organizing phase with alveolar septal fibrosis and type II pneumocyte hyperplasia. Given the difficulties in obtaining a biopsy in patients with ARDS, the presence of DAD is not required to make the diagnosis. However, biopsy and autopsy studies suggest that only one-half of patients who meet the
clinical definition of ARDS also have DAD. The other half are found to have a group of heterogeneous disorders, including pneumonia. Importantly, the subgroup of patients with ARDS who also have DAD appears to have increased mortality. It is possible that the response of these patients to specific therapies targeting the molecular mechanisms of ARDS may differ from patients without DAD. Therefore, it may be important to develop noninvasive methods to identify DAD. A predictive model for DAD based on noninvasive measurements has been developed in an autopsy cohort but must be validated. It would be ideal to identify biomarkers or imaging techniques that help determine which patients with ARDS have DAD. We conclude that additional studies are needed to determine the effect of DAD on outcomes in ARDS, and whether noninvasive techniques to identify DAD should be developed with the goal of determining whether this population responds differently to specific therapies targeting the molecular mechanisms of ARDS.

Take home point: Interesting perspective, of limited practical value.


Objectives: To report the rate of severe complications and diagnostic outcomes immediately after introduction of transbronchial cryobiopsy into the clinical practice of a single-center, high-volume, interventional pulmonary group at a large academic medical center in the United States.

Methods: We conducted a retrospective review of a case series.

Results: Twenty-five consecutive patients underwent transbronchial cryobiopsy for a variety of indications over a period of 14 weeks. In the absence of a strict protocol, a variety of techniques were employed by four attending interventional pulmonologists and one advanced interventional pulmonology fellow to plan and complete the procedures. Three patients (12%) experienced serious hemorrhage immediately after biopsy, including one patient who survived a life-threatening bleed. Two procedures were complicated by an iatrogenic pneumothorax. One patient experienced hypercapnic respiratory failure shortly after the procedure. A definitive diagnosis was made with 14 cryobiopsies (56%). Another five biopsies (20%) contributed to a presumptive diagnosis achieved by multidisciplinary consensus.


Take home point: There are currently ongoing randomized trials investigating the utility of cryobiopsy versus surgical lung biopsy. While the ideal patient population and procedural aspects of cryobiopsy are investigated, it would seem advisable that centers performing this procedure also review protocols for the management of potential complications, such as massive bleeding.

CT scanning of the chest is one of the most important imaging modalities available to a pulmonologist. The advent of high-resolution CT scanning of the chest has led to its increasing use. Although chest radiographs are still useful as an initial test, their utility is limited in the diagnosis of lung diseases that depend on higher resolution images such as interstitial lung diseases and pulmonary vascular diseases. Several metaphoric chest CT scan signs have been described linking abnormal imaging patterns to lung diseases. Some of these are specific to a disease, whereas others help narrow the differential diagnosis. Recognizing these imaging patterns and CT scan signs are thus vitally important. In the present article, we describe a comprehensive list of the commonly encountered metaphoric chest CT scan signs and their clinical relevance.

An excellent review article which is also very entertaining and easy to read


ABSTRACT
Management of systemic vasculitis has been revolutionised over the last decade with the introduction of targeted biological agents. With an increase in both the prevalence and the recognition of vasculitis as well as the high cost of these agents, it is important to ensure their most optimal utilisation. The goals of vasculitis therapy include the induction and maintenance of remissions, preventing relapses, reducing the toxicity of therapy with the aim of reducing morbidity and mortality as well as improving the quality of life of those afflicted. This review focuses on the recent advances in the diagnosis, surveillance and treatment of these conditions.

An update which has a few interesting points.


CASE PRESENTATION: An elderly man presented to the ED from a nursing care facility after transient loss of consciousness. Three weeks previously, the patient had been diagnosed with a high-grade pancreatic neuroendocrine tumor (NET) with metastases to the liver after being hospitalized for weakness. A chest radiograph at that time had revealed a right upper lobe mass that was presumed to represent a metastatic lesion (Fig 1); CT of the chest demonstrated similar findings (Fig 2). The patient had recovered consciousness on arrival to the ED and was diagnosed clinically as having had a syncopal episode from dehydration due to poor intake. On review of systems, the patient reported shortness of breath and a cough productive of scant mucoid sputum of 1 week’s duration. He had no complaints of fever but complained of weakness and poor appetite. In addition, his medical history was significant for hypertension, diabetes mellitus, and congestive heart failure with systolic dysfunction. He was a former smoker. Prior to his recent illness and hospitalization, he lived at home with his family and was independent in his activities of daily living.