I. ARTICLES FOR DISCUSSION


II. ARTICLES FOR NOTATION
Neoplastic

2. Hutchinson J, Hubbard R, Raghu G. Surgical lung biopsy for interstitial lung disease: when considered necessary, should these be done in larger and experienced centres only? Eur Respir J. 2019 Feb 21;53(2).


**Non-neoplastic**


I. ARTICLES FOR DISCUSSION


**Background:**
Cribriform-patterned adenocarcinoma is currently regarded by the WHO as a variant of acinar adenocarcinoma, but recent studies suggest that it may behave in a more aggressive fashion with a poorer prognosis.

**Methods:**
- 735 Japanese patients with resected lung adenocarcinoma
- Tumors classified using 2015 WHO criteria
- Cribriform noted if present in at least 10% of tumor.
- Tumors restaged according to AJCC 8th Edition
- Recurrence-free probability (RFP) and overall survival (OS) were analyzed

**Results:**
- 54 of 90 acinar-predominant tumors were reclassified as cribriform subtype
- Five-year RFP for cribriform subtype 51%, lower than acinar and papillary subtypes (81% and 80%, respectively), but comparable to solid subtype (48%)
- Five-year OS for cribriform subtype (49%) lower than acinar and papillary subtypes (90% and 81%, respectively)
- Multivariate analysis adjusted for stage showed that the cribriform subtype was an independent poor prognostic factor with worse RFP and OS.

**Authors’ Conclusions:**
The cribriform subtype is an independent poor prognostic factor in patients with resected lung adenocarcinoma.

**TAKE-HOME MESSAGE:**
Cribriform pattern is bad, similar to solid pattern. It may be worth including this in your reports if you see it, with a comment noting its association with worse outcomes.


**Background:**
Lymphoepithelioma-like carcinoma of the lung is a rare EBV-associated carcinoma, and usually looks indistinguishable from its nasopharyngeal counterpart. However, it can sometimes lack significant lymphocytic infiltration, making the diagnosis more challenging.

**Methods:**
- 61 cases of pulmonary lymphoepithelioma-like carcinoma reviewed, ALL in Asian patients.
- Lymphocytic infiltrates quantified.

**Results:**
- Tumors had a morphologically continuous spectrum
- Some poorly differentiated tumors show “classic” features with intense lymphocytic infiltration
- Other tumors show “non-classic” morphology with little lymphocytic infiltration
• Most tumors occur in female and non-smoking patients
• Tumors with low lymphocytic infiltration closely resemble non-keratinizing SqCC and tend to be larger in size, have higher SUVmax on imaging, and exhibit shorter times to recurrence than those with high lymphocytic infiltration
• Other distinctive features include granulomatous inflammation (32% of cases), focal keratinization (4%), STAS (25%), and lepidic growth (4%)
• Patients with tumors exhibiting granulomatous inflammation have favorable outcomes
• The presence of STAS did not correlate with prognosis.

Authors’ Conclusions:
Many EBV-associated lung carcinomas do not resemble “classic” undifferentiated nasopharyngeal carcinoma or lymphoepithelioma. The authors propose using an alternative term, “EBV-associated pulmonary carcinoma”, to encompass the entire morphologic spectrum of this entity.

TAKE-HOME MESSAGE:
Consider doing an EBER stain in any non-keratinizing SqCC occurring in an Asian woman or Asian non-smoker.


Background:
Regulator of telomere length 1 (RTEL1) mutations occur in 5-9% of familial pulmonary fibrosis, but the phenotype of patients with ILD and RTEL1 mutations is poorly understood.

Methods:
• Whole exome sequencing performed in 252 probands with ILD
• All patients with ILD and RTEL1 mutation included
• RTEL1 IHC performed in the lungs of controls, as well as in RTEL1 and telomerase reverse transcriptase (TERT) mutation carriers

Results:
• 35 subjects from 17 families
• Median age at diagnosis of ILD was 53.1 years (range 28.0-80.6)
• The most frequent pulmonary diagnoses were IPF (n=20, 57%), secondary ILD (n=7, 20%) and unclassifiable fibrosis or IPAF (n=7, 20%)
• Median transplant-free and overall survival periods were 39.2 months and 45.3 months, respectively
• Extra-pulmonary manifestations were less frequent as compared to other telomere-related gene mutation carriers.
• Systematic analysis of the literature identified 110 patients with ILD and RTEL1 mutations (including this series), and confirmed heterogeneity of pulmonary phenotype, prevalence of non-idiopathic diseases, and low prevalence of extra-pulmonary manifestations (premature gray hair, cytopenias, liver disease)
• RTEL1 IHC labeled bronchial and alveolar epithelial cells, alveolar macrophages, and lymphocytes, but not fibroblasts

Authors’ Conclusions:
RTEL1 mutations are most frequently associated with IPF, but patients with RTEL1 mutations and ILD can be labeled as other disorders clinically. Extrapulmonary manifestations are uncommon.

TAKE-HOME MESSAGE:
RTEL1-associated ILD can look like a lot of things clinically, radiographically, and histologically, including UIP/IPF, CTD-ILD, chronic HP, and unclassifiable ILD.


Background:
CIC-fused sarcomas are a distinctive group of primitive round cell sarcomas previously lumped in the Ewing sarcoma family as “Ewing-like” round cell sarcomas, but they are distinctive from a clinical and molecular standpoint. Common fusions include CIC-DUX4 and CIC-FOXO4 fusions. However, it was recently reported that CIC-NUTM1 can also occur, in a study of previously unclassified PNETs of the CNS and soft tissues. This raises the possibility of a diagnostic pitfall, if this is confused with NUT carcinoma.

Methods:
The authors report the clinicopathologic and molecular features of 6 CIC-NUTM1 sarcomas.

Results:
- Mean age at diagnosis 6 years (2 to 27 y), 4 males
- Primary tumors were located in the CNS (n=3), paravertebral soft tissue and epidural spaces (n=1, each), and lung (n=1)
- Median overall survival 17.5 months (7 to 37 mo), and all but one patient died of disease.
- All tumors displayed classic features of CIC-DUX4 sarcomas with round cell to epithelioid morphology
- Most tumors expressed ETV4 and NUTM1 (n=5/6 and 6/6, respectively), whereas WT1cter was positive in only 2 cases.
- NUTM1 IHC pattern is homogeneous nuclear, not dot-like nuclear.
- All tested tumors were positive for break-apart FISH for CIC and NUTM1, and fusion transcripts were identified by RNA-sequencing

Authors’ Conclusions:
CIC-NUTM1 sarcomas are a new molecular variant of CIC-fused sarcomas with a predilection for the CNS and usually occurring in kids. It may be confused with NUT carcinoma.

TAKE-HOME MESSAGE:
If you’re not careful, this tumor can be confused with NUT carcinoma. Pay attention to the NUT IHC pattern. NUT carcinomas stain with dot-like nuclear pattern. CIC-NUTM1 sarcomas have a diffuse homogeneous nuclear NUT IHC pattern.


Background:
Thymomas can have unusual growth patterns, making the diagnosis more challenging.
Methods:
Twelve cases of thymomas with prominent alveolar-like growth are presented.

Results:
- The 12 cases were identified during a review of more than 350 thymomas.
- Five women and seven men, between the ages of 48 and 69 years (mean, 58.5 years).
- Symptoms were nonspecific
- Tumors were 3.5 to 5 cm in greatest diameter
- All tumors showed a predominant alveolar-like growth pattern without a significant lymphocytic component
- IHC showed positive staining for pankeratin, CK5/6, and p63
- In 9 patients with follow-up, all 9 are alive with no evidence of recurrence.

Authors’ Conclusions:
Thymomas can sometimes have a prominent alveolar-like growth pattern.

TAKE-HOME MESSAGE:
Thymomas can sometimes have a prominent alveolar-like growth pattern.
II. ARTICLES FOR NOTATION

Neoplastic


Activating driver mutations of EGFR, KRAS, and BRAF are usually mutually exclusive in lung cancer, but coexisting mutations can occasionally occur, as the authors nicely confirm. Identification of 2 driver mutations should always be viewed with suspicion and the possibility of laboratory error should be investigated, but sometimes 2 driver mutations are actually present, and they can be in the same tumor cell population or two separate populations.

2. Hutchinson J, Hubbard R, Raghu G. Surgical lung biopsy for interstitial lung disease: when considered necessary, should these be done in larger and experienced centres only? Eur Respir J. 2019 Feb 21;53(2).

An interesting editorial, without a definite answer to the question posed in the title.


This is the first report of a very interesting low-grade myxoid sarcoma with EWSR1-CREB1 fusion arising within the lumen of the main pulmonary artery trunk of a 21 y.o. woman. Although it very closely resembles a primary pulmonary myxoid sarcoma, it also demonstrated keratin expression and is not in the lung. Could this be a myxoid AFH at a strange site, a variant of PPMS, or something else entirely? Only time will tell.


Tissue microarrays were used to test expression patterns in pulmonary adenocarcinomas, SqCCs, metastatic colorectal adenocarcinomas, and metastatic renal cell and breast carcinomas. Not surprisingly, overlapping immunoprofiles can occur in some cases.


Spectral histopathology is a fascinating imaging method based on detection of changes in biochemical composition. A surprising amount of insightful information can be seen using this technique that mirrors standard histopathology. Check it out.


L-type amino acid transporter 1 (LAT1) and 4F2 cell surface antigen (4F2hc) are highly expressed in pleomorphic carcinomas of the lung and are independently associated with worse prognosis.
7. Shaukat I, et al. Detection of RAS and RAS-associated alterations in primary lung adenocarcinomas. A correlation between molecular findings and tumor characteristics. Hum Pathol. 2019 Feb;84:18-25. KRAS, BRAF, NRAS, and PIK3CA mutations are more commonly seen in smokers and were more common in this study than in previous series.

8. Xu S, et al. SOX11: a potentially useful marker in surgical pathology: a systematic analysis of SOX11 expression in epithelial and non-epithelial tumours. Histopathology. 2019 Feb;74(3):391-405. Our hemepath colleagues already use SOX11 routinely to diagnose mantle cell lymphomas and a few other lymphomas. Did you know it also stains other tumors? SOX11 always stains Ewing/PNET and most other neuroectodermal tumors, but it also stains 68% of small cell carcinomas in the lung, 39% of LCNEC, and rare atypical carcinoids (8%), but never typical carcinoids. Rare pulmonary adenocarcinomas (2%) and large cell carcinomas (4%) also stain. Almost all salivary duct carcinomas stain with SOX11, too, along with a few other tumors. There might be some uses for this marker for the pulmonary pathologist, especially if you already have this available in your lab. Might be worth glancing at the tables in this paper if you’re interested.


Non-neoplastic
1. Fisher JH, et al. Procedure volume and mortality after surgical lung biopsy in interstitial lung disease. Eur Respir J. 2019 Feb 21;53(2). Surgical lung biopsies performed at larger centers with higher volumes are associated with lower odds of 30-day post-operative mortality, especially cases that are non-elective.


4. Lee JS, Fischer A. POINT: Does Interstitial Pneumonia With Autoimmune Features Represent a Distinct Class of Patients With Idiopathic Interstitial Pneumonia? Yes. Chest. 2019 Feb;155(2):258-260. A fascinating point and counterpoint discussion regarding the merits or lack thereof surrounding the term “IPAF”. Also see Articles 5, 6, and 7, below. Do you like IPAF as a term, or do you
hate it? Or do you fall somewhere in the middle? Maybe this discussion will help you rethink your position… or maybe not.

