Pulmonary Pathology Journal Club

January 29, 2024

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Articles for Discussion

1. Parrack PH, Hornick JL, Sholl LM. PAX1 expression in thymic epithelial neoplasms and morphologic mimics. *Hum Pathol*. 2023;142:7-14.

Background: Thymic epithelial neoplasms are morphologically diverse and can pose a diagnostic challenge that is complicated by a lack of immunohistochemistry (IHC) markers that are entirely sensitive and specific for thymic epithelium. Polyclonal PAX8 is often used in this context, but it is not a specific marker. The PAX1 transcription factor shares significant homology with PAX8 and plays an integral role in thymic development in humans and murine models. This study evaluated the role of PAX1 IHC in differentiating thymic epithelial neoplasms from morphologic mimics on whole slide tissue sections.

Methods: 100 thymic neoplasms (thymomas, thymic carcinomas, thymic neuroendocrine tumors) and 119 morphologic mimics (squamous cell carcinomas from other sites, lung carcinoids, sarcomatoid mesotheliomas, Ewing sarcomas, lung metastases, and other tumor types) were identified. H&E sections were reviewed by two authors and PAX1 IHC was performed. H-score (0-300) was calculated using percentage and intensity (high / moderate / weak / negative) by author consensus.

Results: The PAX1 antibody stained all 74 thymoma cases; however, there was wide variability in staining intensity within each subtype. The antibody was less sensitive in thymic carcinomas and thymic neuroendocrine tumors compared to thymomas and demonstrated weak staining in a subset of morphologic mimics (21 squamous cell carcinomas, 6 pulmonary neuroendocrine tumors, 1 mesothelioma, 1 lymphoblastic lymphoma, and 1 granulosa cell tumor). With a H-score positive threshold of 75, the antibody had 100% specificity, and sensitivities of 92%, 56%, and 47% in thymomas, thymic neuroendocrine tumors, and thymic carcinomas respectively. The PAX1 antibody showed frequent geographic reduction in staining consistent with compromised antigenicity from variable formalin fixation.

Conclusion: PAX1 IHC has a moderate-to-high sensitivity for thymic epithelial neoplasms; however, the wide staining variability and fixation effects may lead to difficulty with consistent interpretation.

Take home message: This marker is unlikely to supplant the role of PAX8 in diagnostic practice, but it may be a useful addition to immunohistochemistry panels when evaluating for thymic primary tumors.

2. Xing J, Yadav R, Ntiamoah P, et al. Airway injury caused by aspiration of iron sulfate pills: a series of 11 cases. *Mod Pathol*. 2023;36:100347.

Background: It is not widely recognized that iron (ferrous sulfate) pill aspiration causes airway damage. Clinical diagnosis is challenging because patients are often unaware that they have aspirated a pill. The literature on this entity consists mainly of case reports. The aim of this study was to describe the clinical and pathologic features of iron pill aspiration in a series of 11 patients.

Methods: A retrospective review of the authors' pathology archives was performed to identify cases of iron pill aspiration (2013-2023). All available histologic and cytologic material was rereviewed. Clinical information was collected from the electronic medical record, and imaging studies were re-reviewed.

Results: Eighteen endobronchial biopsies were identified from 11 patients (7 women and 4 men; mean age, 70 years; range, 44-82 years). Eight patients had corresponding cytology (20 specimens). Medication history was available in 9 of 11 patients, all of whom were taking iron sulfate pills. Two patients reported possible aspiration episodes; 4 had risk factors for aspiration. The diagnosis of iron pill aspiration was suspected prior to biopsy in only 1 case. Histologically, iron pill particles were yellow, golden brown, or gray, were elongated and crystal or fiber like, and stained strongly with an iron stain. Common histologic findings included mucosal ulceration, acute and/or chronic inflammation, fibrosis, and squamous metaplasia. Iron pill particles were also identified in 11 cytology specimens from 6 patients. On Papanicolaou staining, iron pill particles were yellow to golden, fiber like, refractile, and crystalline. Reactive epithelial cells, squamous metaplasia, and acute inflammation were common.

Conclusion: The combination of iron pill intake and discolored mucosa on bronchoscopy is a potential clue to the diagnosis of iron pill aspiration. Pathologists should familiarize themselves with the appearance of iron pill particles in endobronchial biopsies and cytology specimens from the respiratory tract as this diagnosis is seldom suspected on clinical grounds, and most patients lack a history of aspiration.
Take home message: Take a look at the photos of iron pill fragments in transbronchial biopsies and burn them into your memory. It might come in handy later.

3. Marinescu DC, Hague CJ, Muller NL, et al. Integration and application of radiologic patterns from clinical practice guidelines on idiopathic pulmonary fibrosis and fibrotic hypersensitivity pneumonitis. *Chest*. 2023;164:1466-75.

Background: Clinical practice guidelines separately describe radiologic patterns of UIP and fibrotic HP, without direction on whether or how to apply these approaches concurrently within a single patient. It remains unclear how radiologists can integrate guideline-defined radiologic patterns to diagnose ILD and what the pitfalls are that may be associated with described patterns that require reassessment in future guidelines.
Methods: Patients from the Canadian Registry for Pulmonary Fibrosis underwent detailed reevaluation in standardized multidisciplinary discussion. CT scan features were quantified by

chest radiologists masked to clinical data, and guideline-defined patterns were assigned. Clinical data then were provided to the radiologist and an ILD clinician, who jointly determined the leading diagnosis.

Results: Clinical-radiologic diagnosis in 1,593 patients was IPF in 26%, fibrotic HP in 12%, CTD-ILD in 34%, IPAF in 12%, and unclassifiable ILD in 10%. Typical and probable UIP patterns corresponded to a diagnosis of IPF in 66% and 57% of patients, respectively. "Typical fibrotic HP" radiologic pattern corresponded to a fibrotic HP clinical diagnosis in 65% of patients, whereas "compatible fibrotic HP" radiologic pattern was nonspecific and associated with CTD-ILD or IPAF in 48% of patients. No pattern ruled out CTD-ILD. Gas trapping affecting > 5% of lung parenchyma on expiratory imaging was an important feature broadly separating "compatible" and "typical fibrotic HP" radiologic patterns from other patterns (sensitivity, 0.77; specificity, 0.91).

Conclusion: An integrated approach to guideline-defined UIP and fibrotic HP radiologic patterns is feasible and supports > 5% gas trapping as an important branch point. Typical or probable UIP and typical fibrotic HP radiologic patterns have moderate predictive values for a corresponding clinical diagnosis of IPF and fibrotic HP, although occasionally confounded by CTD-ILD; compatible fibrotic HP radiologic is nonspecific.

Take home message: Radiologists continue to struggle with classifying fibrotic ILD accurately and need guidelines for how to use the current consensus guidelines that are as confusing as they are helpful. The field is a mess and is in desperate need for a gold standard. Will pathology continue to play a role here and drive the field forward with breakthrough discoveries, or be left on the sidelines?

4. Tamura Y, Tamura Y, Shigeta A, et al. Adult-onset idiopathic peripheral pulmonary artery stenosis. *Eur Respir J*. 2023;62:2300763.

Background: Peripheral pulmonary artery stenosis (PPS) refers to stenosis of the pulmonary artery from the trunk to the peripheral arteries. Although paediatric PPS is well described, the clinical characteristics of adult-onset idiopathic PPS have not been established. The authors' objective in this study was to characterise the disease profile of adult-onset PPS.

Methods: A large cohort of Japanese patients with adult-onset idiopathic PPS was examined, all of whom underwent pulmonary angiography. Patients with chronic thromboembolic pulmonary hypertension and Takayasu arteritis were excluded. Patient backgrounds, right heart catheterisation findings, imaging findings, and treatment profiles were collected.

Results: 44 patients (median (interquartile range) age 39 (29-57) years; 29 females (65.9%)) with PPS were enrolled from 20 centers in Japan. Angiographically, stenosis of segmental and peripheral pulmonary arteries was observed in 41 (93.2%) and 36 patients (81.8%), respectively. 35 patients (79.5%) received medications approved for pulmonary arterial hypertension and 22 patients (50.0%) received combination therapy. 25 patients (56.8%) underwent transcatheter pulmonary angioplasty. Right heart cath data showed improvements in both mean PA pressure

(44 versus 40 mmHg; p<0.001) and pulmonary vascular resistance (760 versus 514 dyn·s·cm-5; p<0.001) from baseline to final follow-up. The 3-, 5- and 10-year survival rates of patients with PPS were 97.5% (95% CI 83.5-99.6%), 89.0% (95% CI 68.9-96.4%) and 67.0% (95% CI 41.4-83.3%), respectively.

Conclusion: In this study, patients with adult-onset idiopathic PPS presented with segmental and peripheral pulmonary artery stenosis. Although patients had severe pulmonary hypertension at baseline, they showed a favourable treatment response to PAH drugs combined with transcatheter pulmonary angioplasty.

Take home message: Although clinical features of adult-onset idiopathic PPS overlap somewhat with CTEPH, this appears to be a distinctive clinicopathologic entity. This paper is accompanied by a research letter in the same issue of ERJ and also an editorial (SEE articles #1 and #2 under Notation section below). The research letter highlights a strong genetic component to this entity, with a mutation in most patients with adult-onset idiopathic PPS that is shared by patients with moyamoya disease in East Asians. Hopefully there will be a follow-up paper at some point, illustrating pathologic findings in these patients. Keep your eyes open for such cases in lung biopsies or transplants from East Asians.

Articles for Notation

8. Kanezawa M, Shimokawahara H, Tsuji M, et al. The results of genetic analysis and clinical outcomes after stent deployment in adult patients with isolated peripheral pulmonary artery stenosis. *Eur Respir J*. 2023;62:2301511.
Summary: Genetic analysis was performed on the same cohort reported in the separate study published in the same issue of ERJ, included as one of our discussion articles this month. Interestingly, *RNF213* p.Arg4810Lys mutations were identified in 72.5% of the 20 patients tested, a mutation associated with moyamoya disease in East Asians. Most patients were homozygous for this mutation but a few were heterozygous.
Take home message: Isolated peripheral pulmonary artery stenosis may be a distinct clinicopathologic entity with a strong molecular genetic basis.

2. Constantine A, Dimopoulos K, Gerges C, Lang IM. Peripheral pulmonary artery stenosis in adults: a novel type of pulmonary vascular disease with a strong genetic background. *Eur Respir J*. 2023;62:2302085.
Summary: Editorial accompanying two articles in the same issue of ERJ on this topic, including the article by Tamura Y et al. in our list of articles to disuss, and the research letter by Kanezawa M et al. among our articles for notation.

3. Chen P, Rojas RF, Hu X, et al. Pathomic features reveal immune and molecular evolution from lung preneoplasia to invasive adenocarcinoma. *Mod Pathol*. 2023;36:100326.

Summary: The investigators created an AI model from deep learning to distinguish atypical epithelial cells from inflammatory cells in cases of pulmomary AAH, AIS, MIA, and invasive adenocarcinoma. It is hoped that this AI model will facilitate future studies.
Take home message: Deep learning AI models can do interesting things. Whether they will prove to have any clinical or diagnostic utility in the realm of pulmonary adenocarcinoma and distinguishing it from it's presumed precursor lesions remains to be seen.

4. Akram F, Wolf JL, Trandafir TE, et al. Artificial intelligence-based recurrence prediction outperforms classical histopathological methods in pulmonary adenocarcinoma biopsies. *Lung Cancer*. 2023;186:107413.
Summary: An AI model was developed to predict recurrence after surgical resection of pulmonary adenocarcinoma. Using small biopsies, the AI model significantly outperformed traditional histopathology assessment for predicting recurrence in 124 patients.
Take home message: Traditional pathologic assessment of small lung biopsies is only modestly accurate for predicting future tumor behavior and recurrence, which is an unfortunate reality that we all understand; AI models may outperform humans in this task, but further validation is needed.

5. Hocking AJ, Thomas EM, Prabhakaran S, et al. Molecular characterization of testicular mesothelioma and the role of asbestos as a causative factor. *Arch Pathol Lab Med*. 2023;147:1446-50.
Summary: Nine cases of primary mesothelioma of the tunica vaginalis testis are presented. Asbestos exposure was documented in 7 of 9 cases. Histology, immunoprofiling, and molecular profiling showed features similar to mesotheliomas arising at other sites.
Take home message: Mesothelioma of the tunica vaginalis testis is usually associated with asbestos exposure.

6. Wang H, Yan L, Zhu Y, et al. Exploring the molecular features and genetic prognostic factors of pulmonary high-grade neuroendocrine carcinomas. *Hum Pathol*. 2023;142:81-9.
Summary: Molecular features were analyzed in pure and combined forms of both small cell carcinoma and LCNEC, to look for prognostic markers and also diagnostic markers that might be used to distinguish molecular subtypes of LCNEC. Rb loss by IHC was seen in 100% of "small cell carcinoma-like" cases of LCNEC. Mutations in NCOR2 and wild-type SPTA1 were associated with worse progression-free survival.
Take home message: Rb IHC may be useful for distinguishing molecular subtypes of LCNEC.

7. Wein AN, Lin CY, Ritter JH, Bernadt CT. Development and validation of a decision tree for distinguishing pulmonary adenocarcinomas with mucinous features and metastatic colorectal adenocarcinoma. *Cancer Cytopathol*. 2023;131:781-90.
Summary: The authors examined the staining characteristics and heterogeneity of CK7, TTF-1, NapsinA, CK20, CDX2, and SATB2 in resection specimens of pulmonary adenocarcinomas with mucinous features and metastatic colorectal adenocarcinoma.
Take home message: TTF-1, SATB2, CDX2, and CK7 seem to be the best markers to use in a panel if this is your diagnostic dilemma.

8. Weissferdt A. Non-neoplastic thoracic cysts: a clinicopathologic study of 136 cases. *Am J Surg Pathol*. 2023;47:1349-63.
Summary: A series of 136 thoracic cysts were reviewed. Thymic cysts were the most common cysts seen (50 cases), followed by bronchogenic cysts and pleuropericardial cysts.
Take home message: Thymic cysts may be more common than was previously recognized.

9. Boland JM, Larsen BT, Ryan L, et al. Two tumors with combined features of bronchiolar adenoma/ciliated muconodular papillary tumor and sclerosing pneumocytoma. *Am J Clin Pathol*. 2023;160:555-60.
Summary: Two cases showing hybrid features of BA/CPMT and sclerosing pneumocytoma are presented, with peculiar TTF1+ round stromal cells in a lesion morphologically otherwise consistent with a BA/CPMT. One case also showed expression of BRAF V600E by IHC in the glandular component.
Take home message: Hybrid features of BA/CPMT and sclerosing pneumocytoma can occur in some diagnostically challenging lesions, and their relationship to pure BA/CPMT and pure sclerosing pneumocytoma remains unclear.

10. Denize T, Meador CB, Rider AB, et al. Concordance of ASCL1, NEUROD1 and POU2F3 transcription factor-based subtype assignment in paired tumour samples from small cell lung carcinoma. *Histopathology*. 2023;83:912-24.
Summary: Paired samples of small cell lung carcinoma were tested for concordence of expression of markers for subtype assignment, including ASCL1, NEUROD1, and POU2F3. Discordent results were seen about 10% of the time, regardless of sample locations and time elapsed between sampling.
Take home message: Spatiotemporal heterogeneity of small cell lung cancer may limit concordence in transcription factor-based subtyping by IHC.

Case Reports, Reviews, and Editorials

1. Roden AC, Judge M, den Bakker MA, et al. Dataset for reporting of thymic epithelial tumours: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histopathology*. 2023;83:967-80.
Summary: A nice review of changes in the WHO classification of thymic epithelial and neuroendocrine tumors and key reporting elements as defined by the ICCR. Staging issues are also discussed.

2. Nützinger J, Lee JB, Low JL, et al. Management of HER2 alterations in non-small cell lung cancer – the past, present, and future. *Lung Cancer*. 2023;186:107385.
Summary: Excellent review of the current state of the field regarding Her2 in NSCLC. Includes a comprehensive list of current trials on Her2-directed therapies for NSCLC.

3. Field AS, Pitman M, Cree IA, et al. The rationale for the development and publication of the World Health Organization reporting systems for cytopathology and a brief overview of the first editions of the lung and pancreaticobiliary systems. *Cancer Cytopathol*. 2023;131:751-61.

Summary: A nice review of the new WHO reporting system for lung (and pancreaticobiliary) cytopathology. For those who don't know, it basically mirrors reporting systems for cytopathology of other organs (categories include: non-diagnostic, benign, atypical, suspicious, malignant). No surprises here!

4. Steinberg AW, Zeba F, Rassias AJ, Mota P. A 56-year-old man with progressive subacute hypoxemia. *Chest*. 2023;164:e169-72.
Summary: A case of pulmonary blastomycosis progressing to ARDS.

5. Sumi T, Terai K, Suzuki K, et al. Minocycline-induced acute fibrinous and organizing pneumonia. *Am J Respir Crit Care Med*. 2023;208:e47-8.
Summary: A case of fatal minocycline-induced lung toxicity showing AFOP at autopsy.

6. Nathani A, Tauquir A, Khan S, et al. Unusual presentation of *Pneumocyctis jirovecii* pneumonia in an immunocompromised host. *Am J Respir Crit Care Med*. 2023;208:e44-6.
Summary: PCP presenting as cavitary masses. Nice CT images.

7. Vitlarov N, Burtscher E, Pfeiffenberger E, et al. Peritoneal papillary mesothelioma in situ: *BAP1* mutation with indolent behavior for 15 years. *Virchows Archiv*. 2023:483:873-8.
Summary: The title says it all. Not all cases follow a rapidly progressive course.

8. Kawachi R, Nakatani Y, Furuya M, et al. Pulmonary interstitial glycogenosis in Birt-Hogg-Dubé syndrome-associated lung cysts: a new insight into the pathogenesis? *Pathol Int*. 2023;73:601-8.
Summary: A curoius case of BHD in a young woman having lung cysts that showed some evidence of PIG in the cyst walls.

9. Trisolini R, Pasciuto G, Cancellieri A, et al. Peripheral airway sarcoidosis: seeing what was previously invisible. *Am J Respir Crit Care Med*. 2023;208:1328-9.
Summary: Interesting images of distal airways using ultrathin bronchoscopy. This is the first description of the visual appearance of sarcoidosis involving distal airways using this new bronchoscopy technique.

10. Ikeda O, Shimizu K, Yamada Y, et al. Post-traumatic pulmonary hematoma presenting as multiple ring-shaped spherical nodules. *Am J Respir Crit Care Med*. 2023;208:1227-30.
Summary: Are you tempted to buy a motorcycle? Read this first. The CT images are very interesting… ring-shaped nodular hematomas after a motorcycle accident.

11. Usman S, Haseeb S, Khan MJ, Weber A. A 65-year-old man with concerns of hemoptysis after recent motor vehicle accident and blunt trauma to chest. *Chest*. 2023;164:e173-6.
Summary: Are you tempted to buy a car? Well… bad things can happen when you crash your car, too. Nice CT images of a traumatic pulmonary pseudocyst.