PULMONARY PATHOLOGY JOURNAL CLUB
(November 2024 articles)
December 16, 2024
Kelly J. Butnor, MD
University of Vermont

I. Critical Reviews for Discussion

Garlin-Politis M. et al. Spread through air spaces: interresponder agreement and comparison between pulmonary and general pathologists. Mod Pathol 2024;37:100596

Purpose: To assess interobserver agreement in the interpretation of STAS (as defined in the current WHO Classification) versus artifacts, identify areas of discrepancy in this distinction, and compare the performance between pulmonary and general pathologists.

Methods: The authors created an online survey consisting of 14 questions in which participants were asked whether the findings depicted in an illustration(s) (one question had 3 illustrations) represented STAS or not. The illustrations depicted various patterns (solid, micropapillary) and distributions (continuous, discontinuous, single clusters, multiple clusters) of STAS, artifacts (strips of ciliated respiratory epithelium, tumor clusters with a jagged edge), or mixtures thereof.

Results: There were 136 participants, 6 of whom were trainees. Most (70.6%) practiced pulmonary pathology and were in an academic setting (64.7%). Highest agreement was for recognizing solid and micropapillary tumor clusters ≥ 3 alveolar spaces from the main tumor edge (91.5%) as STAS and strips of ciliated cells as artifacts (97.7%). Agreement did not significantly differ between pulmonary and general pathologists. There was less consensus in recognizing jagged-edged clusters as artifact (57.7%) and in recognizing STAS when no (36.2%) or only 1 alveolar space (73.1%) separated a tumor cluster from the edge of the main tumor. For questions illustrating classic patterns of STAS, overall agreement was 79.2%.

Discussion: This illustration-based survey highlights the need for further clarification of the criteria used to define STAS in order to achieve greater reproducibility. Areas requiring more clarity include: 1) minimum number of tumor cell clusters needed (i.e., > 1 cluster), 2) whether clusters in the first alveolar space from the main tumor edge constitute STAS. The findings also demonstrate that co-occurrence of STAS and artifacts is underrecognized.

Take Home Message: If you are struggling with classifying something as STAS or not, you are not alone! Hopefully, the WHO will more explicitly clarify the definition of STAS in a future edition.

Gagné A, et al. Reporting of incidental thrombotic arteriopathy in lung resection specimens: examination of clinical impact. Am J Surg Pathol 2024;48:1448–1454

Purpose: The prevalence of pulmonary thrombotic arteriopathy (PTA), a manifestation of emboli in the lung, is largely based on historical data from autopsies. This study aimed to determine its prevalence in surgical specimens, correlate the histologic characteristics of PTA with clinically

detected thromboembolic disease, and assess the impact of reporting these findings on clinical management.

Methods: Consecutive lung surgical resections between 2019 and 2022 at a single academic medical center in which incidental PTA was reported were retrospectively reviewed. The histologic characteristics of the thrombi, including temporality (acute, organizing, late), volume (estimated by dividing # of thrombi/# slides containing lung parenchyma), size of affected vessel(s), and distance to tumor in cancer cases, were assessed. The presence of associated infarcts and hypertensive changes was also recorded.

Results: Out of 2930 resections, 2.3% (n=66) were reported to have PTA. A slight female majority (57.6%) was noted. The mean age was 63 years. Most were former smokers (62.1%). The upper lobe was involved in nearly two-thirds of cases. The indication for resection was most commonly cancer (68.2%), while 9.1% were for ILD. None of the identified patients had known hypercoagulability. In 9.1% of cases, there was a history of pulmonary hypertension.

The average number of thrombi per case was 15. Most cases showed thrombi of varying age, while 40.9% had only remote thrombi. Thrombi involving only small to medium arteries was most common. Large artery involvement was seen in only 19.7% of cases. Infarct was present in half of cases and about half showed hypertensive changes. In cancer cases, thrombi were most commonly distant from the tumor. Of the 36.4% of patients with a preceding or subsequent clinical recognized thromboembolic event, a significant portion had PTA of varying age and involvement of large arteries.

Of the 46 of patients with no known history of thromboembolic disease, documentation of PTA in the pathology report prompted further clinical work-up in only 6, which confirmed systemic thromboembolic disease in 2. Additionally, 2 patients who did not receive additional work-up subsequently developed pulmonary embolism.

Discussion: Incidental PTA is detected in ~ 2% of lung resections, two-thirds of which have no clinical suspicion of thromboembolic disease. The reporting of incidental PTA in resection specimens rarely leads to additional work-up and as a result, thromboembolic disease in these patients is underdiagnosed.

Take Home Message: Report findings of PTA in lung resection specimens, particularly acute and organizing changes and those involving large arteries. As they may be clinically significant, it is important to communicate these findings to the clinician.

Villalba JA, et al. Clinicopathologic and molecular characteristics of resected thoracic mass lesions in the pediatric population: a 25-year institutional experience from a tertiary care center. Arch Pathol Lab Med 2024;148:1209–1217

Purpose: To better define the clinicopathologic spectrum of resected thoracic masses in children and genetic alterations in resected primary pediatric lung neoplasms.

Methods: A retrospective search for all thoracic mass lesions resected during a 25-year period in patients ≤ 21 years was conducted at a tertiary general hospital. Primary tumors with adequate tissue were subjected to comprehensive genomic analysis.

Results: There were 385 lesions resected from 373 patients. The ratio of resected nonneoplastic to primary neoplastic lesions was 5.9:1. The ratio of metastatic to primary tumors was 5.6:1. Nonneoplastic mass lesions, cysts, and malformations were most common, seen in 46% of patients. Most were detected in patients under surveillance for prior malignancy. Not surprisingly, the median age of patients with cysts and malformations (8 months) was significantly younger than patients with tumors and other nonneoplastic lesions. The most common cysts and malformations were CPAMs, bronchial atria, and sequestrations. Among other nonneoplastic lesions, necrotizing granulomas were most common, many of which were confirmed to have an infectious etiology.

Metastatic tumors were the second most common category (45.3% of patients) with osteosarcoma accounting for 40.2% of all metastases, followed by Ewing sarcoma (11%). Only 24 patients (6.4%) had a primary lung tumor, while 4.3% had a primary extrapulmonary thoracic neoplasm. The median age at resection did not significantly differ among patients with metastases and primary tumors (16-17.6 years). Among primary lung tumors, 58% were malignant. The most common primary lung tumor was carcinoid (42%) (3 of 10 atypical), the majority (80%) of which were endobronchial. Two patients who had a history of prior malignancy, but no known predisposing genetic syndrome had small adenocarcinomas. Of primary extrapulmonary thoracic tumors, 69% were malignant with sarcomas being most common.

No patients with primary lung tumors died during a 70.2-month median follow-up period and most patients with primary extrapulmonary thoracic neoplasms were alive with no evidence of disease at a median follow-up of 81.6 months.

There were 11 primary tumors with adequate tissue for genomic analysis, all of which were microsatellite stable and had a low tumor mutational burden. While some of the pediatric carcinoids had mutations similar to those seen in carcinoids in adults, others had distinct copy-number alterations.

Discussion: Most resected pediatric thoracic mass lesions represent congenital cysts, malformations, other nonneoplastic lesions, or metastases, whereas primary thoracic neoplasms are relatively uncommon.

Take Home Message: When presented with a pediatric thoracic resection, think nonneoplastic or metastases first and have a low threshold for pursuing an infectious cause in fibroinflammatory lesions.

Filipello F, et al. Stereologic consequences of iatrogenic collapse: The morphology of adenocarcinoma in situ overlaps with invasive patterns. Proposal for a necessary modified classification of pulmonary adenocarcinomas. Lung Cancer 2024;197:107987

Purpose: Iatrogenic collapse can cause pseudopapillary and pseudoacinar formations in AIS, which can result in overdiagnosis as invasive adenocarcinoma. The aim of this study was to better understand the complex 3-dimensional morphology of non-mucinous AIS in resection specimens with iatrogenic collapse.

Methods: A cohort of 70 cases (2 institutions each contributing 35 cases) of resected lung adenocarcinoma ≤ 3 cm with adequate follow-up were retrospectively analyzed for a variety of morphometric parameters (fractions of air, tumor cells, and stroma, as well as tumor cell height and length). CK7 and EVG stains were also performed to assess the stroma for features of collapse. A mathematical model was devised to simulate the effects of collapse on morphology.

Results: Of the 70 cases studied, 1 was originally classified as AIS. On review, 9 additional cases were reclassified as iatrogenic collapsed AIS, all of which had 100% recurrence-free survival after a mean follow-up of 69.5 months. Based on the findings, a modified classification of adenocarcinoma was proposed to address issues of collapse, tangential cutting, true invasion, and multilayering falling short of micropapillary, cribriform, and solid alveolar filling growth. Table 1 offers details on histologic features used to distinguish AIS with collapse from true invasion, including patterns of elastin and CK7 staining.

Take Home Message: Beware of overinterpreting infolding of alveolar walls from iatrogenic collapse and the resultant pseudopapillary and pseudoacinar formations as evidence of invasion. True papillae and small acini lack elastin.

II. Summaries for Notation

Möller K, et al. TTF-1 is a highly sensitive but not fully specific marker for pulmonary and thyroidal cancer: a tissue microarray study evaluating more than 17,000 tumors from 152 different tumor entities. Virchows Archiv 2024;485:815–828

Purpose: To better understand the prevalence of TTF-1 immunoreactivity in various tumors and non-neoplastic tissues.

Methods: TTF-1 immunoexpression was assessed in tissue microarrays containing over 17,000 samples from 152 tumor types and 76 different non-neoplastic tissue types using the recombinant rabbit monoclonal TTF-1-antibody clone MSVA-312R from MS Validated Antibodies GmbH, Hamburg, Germany.

Results: In addition to thyroid carcinomas, lung adenocarcinomas, and neuroendocrine tumors, some thymomas (39%), and some mesenchymal tumors (21% of MPNSTs, 17% of Ewing sarcomas, 29% of rhabdomyosarcomas, 20% of rhabdoid tumors, and 42% of schwannomas) stained with this TTF-1 antibody. The sensitivity/specificity for lung adenocarcinoma was 94%/86% with this TTF-1 clone alone and 85%/99% when used in combination with Napsin-A. This TTF-1 clone stained 6% of colorectal, 2% of pancreatic, and 3% of gastric adenocarcinomas.

Take Home Message: The TTF-1-antibody clone MSVA-312R, while sensitive for a diagnosis of lung adenocarcinoma, is not as specific, a limitation that can be improved by using it in conjunction with Napsin-A. This TTF-1 clone stains a small proportion of gastrointestinal carcinomas, which can hamper the distinction from enteric-type lung adenocarcinoma.

It would appear that the clinical utility of this TTF-1 clone remains to be determined, as a prior study comparing TTF-1 clones commonly used in clinical practice found substantially higher specificity (96%) for the 8G7G3/1 clone in the diagnosis of lung adenocarcinoma versus other primary lung carcinomas and metastases (Vidarsdottir H. et al. Am J Clin Pathol 2018;150:533-544).

Weissferdt A and Moran C. PAX5 and CD70 are expressed in thymic carcinoma but not in atypical thymoma (WHO type B3 thymoma): an immunohistochemical analysis of 60 cases. J Clin Pathol 2024;77:761–765.

Purpose: To determine if there are additional immunostains that will differentiate between thymic carcinoma and atypical thymoma, two entities that have morphologic and immunophenotypic overlap.

Methods: Whole tumor slides of thymic carcinoma and atypical thymoma (30 of each) were subjected to a panel of immunostains, including PAX2, PAX5, PAX8 (all monoclonal), as well as CD70.

Results: PAX5 stained most (67%) thymic carcinomas and no atypical thymomas. CD70 also stained most (60%) thymic carcinomas and only 1 (3%) atypical thymoma. PAX8 was negative in all cases and PAX2 stained only 1 (3%) thymic carcinoma.

Take Home Message: PAX5 and CD70 staining is relatively common in thymic carcinoma and unusual in atypical thymoma. This differential staining pattern may aid in separating these entities on small biopsies or when the morphologic features are equivocal.

Husain AN, et al. Guidelines for pathologic diagnosis of mesothelioma: 2023 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2024;148:1251–1271 (and supplementary data file)

This is third (I believe) iteration of this useful resource for the diagnosis of mesothelioma. Tables categorizing the utility of various IHC markers for distinguishing mesothelioma from reactive mesothelial proliferations, as well as metastases of non-mesothelial origin are again included. New to this version are a comprehensive algorithm for tissue diagnosis of mesothelial proliferations (figure 10) and grading criteria for epithelioid pleural mesothelioma (table 6).

Brune MM, et al. MTAP as an emerging biomarker in thoracic malignancies. Lung Canet 2024;197:107963

Nice review summarizing the current literature on the role of MTAP not only in the diagnosis of mesothelioma, but also as an emerging predictive biomarker in NSCLC. MTAP loss, which has been reported in 13% of NSCLC, appears to be a negative predictor of immune checkpoint inhibitor response and a positive predictor of response to protein arginine methyltransferase 5 (PRMT5)-inhibitors in clinical trials. Different testing methods, including IHC, FISH, and NGS are discussed.

Villeneuve T, et al. Images in Pulmonary, Critical Care, Sleep Medicine and the Sciences - Domestic Mixed-Dust Pneumoconiosis. Am J Respir Crit Care Med 2024;210:1267–1268

Striking case of apparent domestically acquired particulate lung disease in an Afghan woman with prolonged exposure to a coal and biomass fuel-burning unventilated indoor stove. She had mixed dust nodules on biopsy, which are shown along with the clinicoradiographic findings in the composite figure in this report, which is worth checking out.