Pulmonary Journal Club

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Articles for Discussion

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1. Higashiyama M et al. Invasive Mucinous Adenocarcinoma of the Lung With a Mural Nodule-like Lesion. Am J Surg Pathol 2022;46:1524–1532

Background: The authors note that mucinous tumors of various sites can rarely develop sarcoma-like nodules, commonly referred to as mural nodules. They are most commonly described in the ovary, especially in association with mucinous borderline tumors, but have also been observed in mucinous carcinomas of other organs including the appendix and pancreas. Ovarian mural nodules are often subtyped into 3 categories: sarcomatoid, anaplastic carcinoma-like, and sarcoma-like. The authors state that the first 2 subtypes are regarded as dedifferentiated lesions based on the clonal relationship with the mucinous tumor whereas sarcoma-like nodules are thought to represent reactive lesions.

The study looks to determine whether invasive mucinous adenocarcinomas (IMA) of the lung can develop mural nodules.

Methods: The authors looked for mural nodule-like lesions in 213 cases of surgically resected IMA of the lung. They defined mural nodule-like lesion as “abrupt discrete lesions showing a dedifferentiated appearance.” They excluded cases that only showed poorly differentiated areas. For cases with mural nodule-like lesions, they look at clinical features, reviewed radiologic and pathologic findings and performed immunohistochemistry for pan-CK, TTF1, HNF4a, and p53. They also performed microdissection of the differentiated IMA and mural-like nodule to run comparative molecular studies.

Results: They identified 11 cases of IMA with foci of dedifferentiation they considered to represent mural nodule-like lesions (5% of their IMA cases); the clinicopathologic features of those cases is presented in table 1. Four cases showed sarcomatoid nodules (Figures 1 and 2), which they classified based on spindle cell predominant histology, sometimes with osteoclast-like giant cells. Two cases showed anaplastic carcinoma nodules (Figure 3), based on the presence of undifferentiated polygonal cells. Five cases were classified as sarcoma-like nodules (Figure 4), based on the presence of spindled and/or large polygonal cells that lack cytokeratin staining.

Demographic features comparing IMA with and without mural nodule-like lesions are presented in table 2. Mural nodules were significantly associated with older age, male sex, and smoking history. Immunohistochemical studies showed that the areas of differentiated IMA were typically positive for HNF4a whereas the mural nodule-like lesions tended to have decreased expression. Molecular studies showed that all pairs of the two components had identical genotypes. Of the 11 cases of IMAs with mural nodules, 2 patients died, 1 relapsed, and the other 8 were disease free; there were no differences in outcomes noted between patients with and without mural nodules but the authors note that the number of cases was small.

Discussion: IMA of the lung can show mural nodules similar to those seen in the ovary. They note that distinguishing between reactive nodules (i.e. sarcoma-like) and neoplastic nodules (i.e. sarcomatoid or anaplastic) using IHC can be difficult.

Comment: It may be worth further study to determine whether this finding has any prognostic significance. I'm also uncertain whether comparison to the ovary is reasonable given that ovarian mural nodules are usually in borderline tumors and that non-mucinous adenocarcinomas of the lung can also show sarcomatoid change.

2. Marina K.Baine et al. POU2F3 in SCLC: Clinicopathologic and Genomic Analysis With a Focus on Its Diagnostic Utility in Neuroendocrine-Low SCLC. Journal of Thoracic Oncology. Volume 17, Issue 9, September 2022, Pages 1109-1121.

Background: POU2F3 is a recent marker of a small cell lung carcinoma (SCLC) subtype related to chemosensory tuft cells (SCLC-P). The characteristics of SCLC-P have not been fully defined, and the data on POU2F3 expression in other lung tumors are scarce.

Methods: We screened 254 SCLC for POU2F3 expression and comprehensively analyzed histopathologic, genomic, and clinical characteristics of POU2F3-positive tumors. We also explored POU2F3 expression in other major lung cancer types (n = 433) and a targeted set of potential diagnostic mimics of SCLC (n = 123).

Results: POU2F3 was expressed in 30 of 254 (12%) SCLC and was strongly associated with low expression of standard neuroendocrine markers (synaptophysin, chromogranin A, CD56, INSM1). Notably, POU2F3 was expressed in 75% of SCLC with entirely negative or minimal neuroendocrine marker expression (15/20) and was helpful in supporting the diagnosis of SCLC in such cases. Broad targeted next-generation sequencing revealed that SCLC-P (n = 12) exhibited enrichment in several alterations, including PTEN inactivation, MYC amplifications, and 20q13 amplifications, but similar rates of RB1 and TP53 alterations as other SCLC (n = 155). Beyond SCLC, POU2F3 expression was exclusively limited to large cell neuroendocrine carcinoma (12%) and basaloid squamous cell carcinoma (22%).

Discussion: This is the largest cohort of SCLC-P clinical samples to date, where the authors describe the diagnostic utility of POU2F3 in a challenging subset of SCLC with low or absent expression of standard neuroendocrine markers. The distinct genomic alterations in SCLC-P may offer a novel avenue for therapeutic targeting. The role of POU2F3 in a narrow subset of other lung cancer types warrants further study.

Comment: POU2F3 expression and tuft cell-like phenotype in SCLC have been described in several prior studies after the initial description in 2018. This is the largest study to date on this distinct subtype of SCLC, significantly expanding the clinicopathologic and genomic characteristics of this subset and providing first evidence for the utility of POU2F3 as an ancillary marker for the diagnosis of NE-low SCLC. This is also the first study to perform a survey of POU2F3 expression by IHC in large cohorts of all other major lung cancer types and several histologic mimics of SCLC (N = 556 tumors in total), confirming a very narrow and specific expression pattern for POU2F3. Having POU2F3 as a positive marker for these NE-minimal/negative SCLC constitutes a valuable addition to the IHC marker arsenal for the diagnosis of SCLC. Notably, we illustrate here several cases with NE-negative or NE-minimal profiles, where robust expression of POU2F3 served as supporting evidence for SCLC diagnosis.

3. Ilyas Yambayev et al. Vascular invasion identifies the most aggressive histologic subset of stage I lung adenocarcinoma: Implications for adjuvant therapy. Lung Cancer. Volume 171, September 2022, Pages 82-89.

Background: Approximately 15% of stage I lung adenocarcinomas will recur despite adequate surgical therapy. Adjuvant therapy may benefit specific high-risk subsets; however, it is unclear which patients are sufficiently predisposed to recurrence to warrant intensified therapy.

Methods: 517 AJCC 8th edition stage I/0 lung adenocarcinomas ≤ 4 cm total size were graded (WHO-2015 and WHO-2021) and compared to stage subgroupings using 7-year recurrence free (RFS), disease specific (DSS), and overall survival (OS). Low malignant potential (LMP) adenocarcinoma was assigned as previously defined. Univariate/multivariate analysis was performed to assess risk factors associated with aggressive behavior.

Results: Vascular invasion was the most significant histologic feature on multivariate analysis for both RFS (HR = 4.68, $p < 0.001$) and DSS (HR = 3.67, $p = 0.001$) and nearly reached

significance for OS (HR = 1.47, p = 0.060). Angioinvasive adenocarcinomas comprised 26 % of the cohort and exhibited a 7-year 64 % RFS, 73 % DSS, and 50 % OS; in contrast to 20 % WHO-2015-G3 (7-year 71 % RFS, 79 % DSS, & 54 % OS), 44 % WHO-2021-G3 (7-year 79 % RFS, 85 % DSS, & 56 % OS), and 21 % stage IB (7-year 72 % RFS, 79 % DSS, and 50 % OS) adenocarcinomas. The majority (>50 %) of overall mortality was disease specific for angioinvasive adenocarcinoma whereas ≤25 % of overall mortality was disease specific for the remaining tumors. Angioinvasive adenocarcinomas were proportionally more common among those still smoking at diagnosis (49 %), male sex (49 %), and black race (16 %) than other subtypes.

Discussion: Vascular invasion is present in 26% of stage I lung adenocarcinoma (LUAD). Vascular invasion is the most predictive histologic feature of stage I LUAD ≤ 4 cm. Angioinvasive stage I LUAD have a 7-year 64% RFS, 73% DSS, and 50% OS. The majority (>50 %) of overall mortality is disease specific for angioinvasive LUAD. The benefit of adjuvant therapy should be studied for stage I angioinvasive LUAD ≤ 4.

Comment: An interesting article discussing the importance of assessing for angioinvasion in lung cancer.

4. Chan Xiang et al. Distinct mutational features across preinvasive and invasive subtypes identified through comprehensive profiling of surgically resected lung adenocarcinoma. Modern Pathology. 35, pages1181–1192 (2022).

Background: The study aimed to understand the unique molecular features of preinvasive to invasive lung adenocarcinoma subtypes.

Methods: The group retrospectively analyzed the clinical, histopathological, and molecular data of 3,254 Chinese patients with preinvasive lesions (n = 252), minimally invasive adenocarcinomas (n = 479), and invasive LUAD (n = 2,523). Molecular data were elucidated using a targeted 68-gene next-generation sequencing panel.

Results: The findings revealed four preinvasive lesion-predominant gene mutations, including MAP2K1 insertion-deletions (indels), BRAF non-V600E kinase mutations, and exon 20 insertions (20ins) in both EGFR and ERBB2, which we referred to as mutations enriched in AIS (MEA). The detection rate of MEA in invasive tumors was relatively lower. MAP2K1 missense mutations, which were likely passenger mutations, co-occurred with oncogenic driver mutations, while small indels were mutually exclusive from other genes regardless of the invasion level. BRAF non-V600E kinase-mutant invasive adenocarcinomas (IAC) had significantly higher mutation rates in tumor suppressor genes but lower frequency of co-occurring oncogenic driver mutations than non-kinase-mutant IAC, suggesting the potential oncogenic activity of BRAF non-V600E kinase mutations albeit weaker than BRAF V600E. Moreover, similar to the extremely low frequency of MAP2K1 indels in IAC, BRAF non-V600E kinase domain mutations co-occurring with TSC1 mutations were exclusively found in preinvasive lesions. Compared with EGFR L858R and exon 19 deletion, patients with preinvasive lesions harboring 20ins in either EGFR or ERBB2 were significantly younger, while those with IAC had similar age. Furthermore, our study demonstrated distinct mutational features for subtypes of oncogene mutations favored by different invasion patterns in adenocarcinomas.

Discussion: The data demonstrates the distinct mutational features between preinvasive lesions and invasive tumors with MEA, suggesting the potential involvement of MEA in the early stages of tumorigenesis. Further pre-clinical studies are required to establish the role of these genes in the malignant transformation of preinvasive lesions into invasive tumors.

Comment: Interesting how many cases of AIS and MIA they identified. The percentages seem unusually high, and I wonder about reproducibility and the impact on their data.

Non-Neoplastic Notations

1. Demitrios Dedousis et al. Comparing Survival in Patients With Lung Cancer With and Without a History of Common Autoimmune Disease. Journal of Heart & Lung Transplantation. VOLUME 3, ISSUE 9, 100375, SEPTEMBER 01, 2022.

Background: Autoimmune disease has both a predisposing and a protective effect toward malignancy. Though studies have investigated the risk of malignancy in patients with autoimmune disease, there is limited research on how autoimmunity affects survival.

Methods: This study compared survival in patients with lung cancer with and without autoimmune disease. Patients with lung cancer were culled from the Surveillance, Epidemiology, and End Results Medicare databases (2007–2014), and autoimmune diseases were identified using diagnosis codes.

Results: The overall prevalence of investigated autoimmune diseases among the 112,445 patients was 22.7%. Overall survival (OS) ($p < 0.0001$) was longer and cancer-specific mortality (CSM) ($p < 0.0001$) reduced among patients with autoimmune disease. Median OS was 5 months higher. Improved OS and CSM were also apparent in disease stages 1, 3, and 4 in the NSCLC and SCLC subgroups ($p < 0.0001$) and across most specific autoimmune diseases. After adjusting for the effects of age, sex, race, disease stage, and chronic kidney disease, autoimmune disease was still predictive of higher OS (hazard ratio = 1.23, 95% confidence interval: 1.21–1.25, $p < 0.0001$) and reduced CSM (hazard ratio = 1.16, 95% confidence interval: 1.14–1.18, $p < 0.0001$).

Discussion: The prevalence of rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematous was highly enriched compared with the general population. The improvement in OS and CSM was larger in NSCLC than in SCLC, suggesting a larger role for the

immune system in NSCLC. Alternate explanations for the improved survival include lead time bias, better access to health care, and a survival or autoimmunity-inducing genetic factors.

Neoplastic Notations

1. Nicholas P.J.Romatowski et al. Endobronchial Ultrasound Transbronchial Needle Aspiration With a 19-Gauge Needle vs 21- and 22-Gauge Needles for Mediastinal Lymphadenopathy. CHEST. Volume 162, Issue 3, September 2022, Pages 712-720.

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is commonly used to evaluate mediastinal lymphadenopathy. Studies focusing on malignant lymphadenopathy have compared 21- and 22-gauge (21G and 22G, respectively) needles and have not identified an advantage of one needle size over the other in terms of diagnostic yield

Methods: This study retrospectively examined records of 730 patients from the Stather Canadian Outcomes Registry for Chest Procedures (SCOPE) database who underwent EBUS-TBNA for a diagnosis of suspected sarcoidosis, lymphoma, or mediastinal lymphadenopathy not yet diagnosed. A propensity score analysis of two groups was performed. One group comprised patients undergoing EBUS-TBNA with a 19G needle, the other with a 21G or 22G needle. Cases for analysis were selected with a 1:2 ratio of 19G vs 21/ 22G using logistic regression and random matching with all eligible 19G cases included

Results: There were 137 patients (312 targets) in the 19G group and 274 patients (631 targets) in the 21/22G group in the propensity score analysis. The diagnostic yield was 107 of 137 (78.1%) in the 19G group vs 194 of 274 (70.8%) in the 21/22G group (difference, 7.3%; 95% CI, –1.9 to 15.6; P ¼ .116). The sensitivity of EBUS-TBNA for sarcoidosis was 80 of 83 (96.4%) in the 19G group vs 150 of 156 (96.2%) in the 21/22G group (difference, 0.24%; 95% CI, –6.6 to 85.1; P ¼ .93). In patients with a final diagnosis of lymphoma, EBUS was diagnostic in 10 of 13 (76.9%) in the 19G group vs 12 of 12 (100%) in the 21/22G group (difference, 23.1%; 95% CI, –5.4 to 50.3; P ¼ .08).

Discussion: According to this study there is no statistical difference in the larger gauge needles in terms of diagnostic yield for the diagnose of lymphoma and sarcoidosis. We will have to do more with less!

2. Pablo Perez Castro et al. Importance of tumor size in resectable stage III-N2 non–small cell lung cancer. Journal of Thoracic and Cardiovascular Surgery. Volume 164, Issue 3, September 2022, Pages 629-636.

Background: The 8th TNM edition classifies stage III-N2 disease as IIIA and IIIB based on a tumor size cutoff of 5 cm. However, the importance of tumor size on survival in patients with resectable stage III-N2 disease has not been analyzed systematically.

Methods: Survival analysis based on tumor size (>5 cm vs ≤ 5 cm) for 255 consecutive patients with nonbulky (maximal lymph node diameter of 1.5 cm) stage III-N2 non–small cell lung cancer treated with surgery in our institution.

Results: Ninety patients (35.3%) underwent induction chemoradiation therapy (n = 72, 28%) or induction chemotherapy (n = 18, 7%), and 165 patients underwent primary surgery followed by adjuvant chemotherapy (n = 52, 32%), adjuvant chemoradiation therapy (n = 47, 29%), or adjuvant radiation therapy (n = 14, 13.2%). After a median follow-up of 6.5 years, the overall survival was 46.5% at 5 years and 28.9% at 10 years. In tumors 5 cm or less, there was no difference in survival between patients treated with induction or adjuvant therapy. However, in tumors greater than 5 cm, the survival was significantly better after induction therapy compared with adjuvant therapy or surgery alone. Pathologic multi-station N2 disease was more frequently detected in tumors greater than 5 cm (31% vs 18% in tumors ≤5 cm, P = .042), and the rate of R1 resection was lower after induction therapy (2.2% vs 8.5% in primary surgery, P = .048).

Discussion: These results support the redefinition of tumors greater than 5 cm with resectable N2 disease to stage IIIB. This article nicely highlights again the importance of accurate measurements in lung cancer.

Case Reports, Editorials, and Reviews

1. Marissa O'Callaghan et al. A Man With Malaise, Myalgia, and Rapidly Progressive Interstitial Lung Disease. CHEST Volume 162, Issue 3, September 2022, Pages e111-e116.

Summary: A 45-year-old man sought treatment at the ED during the third wave of the COVID 19 pandemic with a month-long history of fatigue, cough, myalgia, and hand stiffness. He was found to have interstitial lung disease associated with anti-melanoma differentiation-associated protein 5 (MDA5) dermatomyositis

2. Andrew P.Stein et al. A 43-Year-Old Woman With Pleuritic Chest Pain, Shortness of Breath, and Weakness of All Extremities. CHEST. Volume 162, Issue 3, September 2022, Pages e117-e121.

Summary: A 43-year-old woman with a medical history of hypothyroidism, psoriasis, and tobacco abuse (30-pack year history) who had quit smoking several months prior to presentation presented with pleuritic chest pain. She also noted a 2-year history of progressive numbness and weakness in her bilateral upper and lower extremities that now prevented her from completing her activities of daily living. She had worsening exertional dyspnea and a subjective 50-lb weight loss over the past year. She was found to have pulmonary and neurodegenerative Langerhans cell histiocytosis.

3. Andrew J .Arifin and David A. Palma. The changing landscape of pneumonitis in non-small cell lung cancer. Volume 171, September 2022, Pages 1-2.

Summary: New treatment modalities can have overlapping toxicity profiles, and pneumonitis is a particular toxicity of concern. Pneumonitis can be caused by radiation, cytotoxic chemotherapy, targeted agents, and checkpoint immunotherapy. The risk of pneumonitis was low, with an estimated pooled incidence of grade 3 or higher radiation pneumonitis of 3.62% (95% confidence intervals [CI]: 1.65–6.21) in randomized trials and 5.98% (95% CI: 2.26–12.91)

in observational, real-world studies. The most common chemotherapy agents used were cisplatin-pemetrexed (4 of 6 randomized trials) and carboplatin-paclitaxel (4 of 8 observational studies).

These rates of pneumonitis are lower than those reported in prior years, likely due to improvements in radiation technology.

4. Majd Khasawneh et al. A 65-Year-Old Woman With Intractable Cough. CHEST Volume 162, Issue 3, September 2022, Pages e123-e126.

Summary: A 65-year-old woman was referred for a second opinion regarding a 7-month history of a persistent, progressive, nonproductive cough. She was found to have a retrosternal multinodular goiter causing her chronic cough.

5. Nicoletta Golfi et al. A 35-Year-Old Man With Fever, Cough, and Erythematous-Erosive Mucous Membrane Lesions Accompanied by a Generalized Cutaneous Rash. CHEST. Volume 162, Issue 3, September 2022, Pages e139-e143

Summary: Mycoplasma pneumoniae-induced Stevens-Johnson Syndrome (MP-SJS) in a patient who presented with a 7-day history of fever and cough.

6. Manana Javey and Stephanie J.Yaung. Incorporating Genetic Biomarkers in WHO Classification of Lung Cancer. Journal of Thoracic Oncology. Volume 17, Issue 9, September 2022, Pages e79-e80.

Summary: The authors raise the point that as genetic alterations are not incorporated into current classification (ie. “invasive mucinous adenocarcinoma of the lung with ALK rearrangement” instead of “invasive mucinous adenocarcinoma of the lung”) then there is less of an emphasis on molecular studies and that tissue is often wasted in pursuit of a histologic diagnosis rather than a search for molecular diagnosis (and possibly targeted treatment).

7. Ryota Matsuoka et al. Determining Whether YAP1 and POU2F3 Are Antineuroendocrine Factors. Journal of Thoracic Oncology. Volume 17, Issue 9, September 2022, Pages 1070-1073.

Summary: While there is meaningful data on POU2F3 expression in primary lung tumors, further genomic, transcriptomic, epigenetic, and proteomic analyses of POU2F3-expressing tumors with NE and non-NE features will be needed to understand the clinicopathologic significance of POU2F3.

8. Andrew G.Nicholson et al. 2021 WHO Classification of Lung Cancer: A Globally Applicable and Molecular Biomarker-Relevant Classification. Journal of Thoracic Oncology. Volume 17, Issue 9, September 2022, Pages e80-e83.

Summary: This a response editorial to the editorial questioning why molecular alterations are not utilized in the WHO for Thoracic Tumors as they are in the WHO for brain tumors. The authors reiterate that in comparison to past WHO editions for thoracic tumors that molecular studies are markedly emphasized, that many lung tumors are not diagnosed by specialists, and that in many countries molecular techniques may not be available, and so, the decision was made not to require the molecular alterations as part of the tumor diagnoses.

9. Steinar Solberg et al. Concordance between clinical and pathology TNM-staging in lung cancer. Lung Cancer. Volume 171, September 2022, Pages 65-69.

Summary: There is a low concordance between the cTNM and pTNM staging in lung cancer. There is a low concordance between cT and pT descriptors. The differences in tumour diameter reported in the clinical and the pathology notifications were ≤5 mm and ≤10 mm in 65.9 % and in 84.4 % of the cases, respectively. For the c- and pT categories, there was concordance in 53.4 % while 28.4 % were upstaged and 18.2 % were downstaged. For N categories there was concordance in 83.3 % while 13.7 % were upstaged and 3.0 % were downstaged. Unforeseen

pN2 was found in 6.2 % of the cases. For TNM staging groups there was concordance in 48.1 % of the cases, while 33.4 % were upstaged and 18.5 % were downstaged. The calculated sensitivity and specificity for reported cTNM staging as diagnostic test for being eligible for adjuvant treatment (stage II–IIIA) were 0.65 and 0.91, respectively.

10. Kyung Soo Lee and Yunjoo Im. Traction Bronchiectasis and Bronchiolectasis at CT Predicts Survival in Individuals with Interstitial Lung Abnormalities. Radiology. 2022 Sep;304(3):702-703.

Summary: Individuals in the COPDGene cohort with interstitial lung abnormalities who showed traction bronchiectasis and/or bronchiolectasis on CT images had poorer clinical outcomes than those without.

11. Frédérique Penault-Llorca et al. Expert opinion on NSCLC small specimen biomarker testing — Part 1: Tissue collection and management. Virchows Archiv volume 481, pages335–350 (2022)

Summary: Tissue sparing techniques, including the 'one biopsy per block' approach and small sample cutting protocols, can help preserve tissue. Cytological material (formalin-fixed paraffin-embedded [FFPE] cytology blocks and non-FFPE samples such as smears and touch preparations) can be an excellent source of nucleic acid, providing either primary or supplementary patient material to complete morphological and molecular diagnoses.

12. Frédérique Penault-Llorca et al. Expert opinion on NSCLC small specimen biomarker testing — Part 2: Analysis, reporting, and quality assessment. Virchows Archiv volume 481, pages351–366 (2022).

Summary: Molecular testing reports should include clinical interpretation with additional commentary on sample adequacy as appropriate. Molecular tumour boards are recommended to facilitate the interpretation of complex genetic information arising from NGS, and to

collaboratively determine the optimal treatment for patients with NSCLC. Finally, whichever testing modality is employed, it is essential that adequate internal and external validation and quality control measures are implemented.