I. Articles for Discussion


**Purpose:** To report the spectrum of histopathologic findings in treated or treatment-naïve patients with psoriasis or psoriatic arthritis and diffuse parenchymal lung disease (DPLD).

**Methods:** Cases were identified in the Mayo Clinic consultation files from patients with psoriasis or psoriatic arthritis and DPLD who had undergone VATS biopsy (which represented 0.2% of approximately 25,600 cases over a 7½-year period). Those with evidence of active infection or interstitial lung disease referable only to smoking were excluded.

**Results:** The study comprised 44 patients with a median age of 60 years, half of whom were women. Most (61%) had psoriatic arthritis and the rest had psoriasis alone. Adequate clinical information was available in 30 patients, 23% of whom had a concomitant connective tissue disease (CTD), while another 23% had features suggestive of undiagnosed CTD. Most patients (70%) presented with non-specific respiratory symptoms >5 years (mean, 13.8 years) after being diagnosed with psoriasis or psoriatic arthritis. Among patients for whom adequate exposure history was available, 30% had potential inhaled antigen exposure, but none met definite or probable/provisional hypersensitivity pneumonitis consensus criteria. About one-third (32%) of patients had no history of prior systemic therapy, but all patients with CTD in which adequate history was available did. The most common radiographic manifestation were ground-glass opacities, consolidation, and/or reticulations that were most commonly lower-lobe predominant. Mosaicism/air-trapping and honeycombing were equally uncommon (17%).

Almost all (98%) showed histologic changes of chronic lung disease with NSIP being the most common pattern (55%), followed by unclassifiable fibrosis (18%) (see Table 4). Accompanying lymphoid infiltrates and aggregates were common, as was chronic bronchiolitis and small airways remodeling. Acute lung injury, usually organizing pneumonia, was seen in over half of patients (62%), nearly always superimposed on chronic injury. Nearly all patients with DAD or AFOP had received prior immunomodulatory therapy. Granulomas, typically rare, poorly formed, interstitial, and non-necrotizing, were seen in 39% of patients. While eosinophils were common, they were usually sparse and interstitial. No significant difference in the histologic findings was seen between patients with or without concomitant CTDs or prior therapy.

**Discussion:** Some patients with psoriasis or psoriatic arthritis, even those who are treatment-naïve, develop significant DPLD. It is difficult to exclude adverse drug reaction as a potential contributor in patients who have received prior treatment. NSIP with or without OP is the most common histologic manifestation.

**Take Home Message:** Add psoriasis and psoriatic arthritis to the list of causes of ILD!

Purpose: To report the clinicopathologic findings in a series of pleural and peritoneal mesothelial in situ (MIS) lesions that morphologically mimic well-differentiated papillary mesothelial tumor (WDPMT).

Methods: Cases that histologically resembled WDPMT, but showed BAP1 loss were selected from the authors' consultation files.

Results: Eight cases (3 pleural, 5 peritoneal) cases were identified (see Table 2). Two of the pleural cases were in men and the remainder of cases were in women. The patients with pleural lesions ranged from 66-78 years and peritoneal were 31-81 years. All 3 pleural cases were associated with effusion without radiographic evidence of tumor. Four peritoneal cases had ascites and nodular lesions, while the fifth presented as an umbilical mass. Histologically, the lesions were described as “looking like diffuse WDMPT,” but with immunohistochemical loss of BAP1, which was also seen in the associated flat mesothelium (see Figure 1C). In all 3 pleural cases, there were “occasional microscopic foci of superficial invasion” (see Figure 1D). This same finding and/or “single nodules of invasive mesothelioma” were present in all 5 peritoneal cases (see Figures 2C and 3C). Clinical findings of invasive mesothelioma developed in all 3 pleural cases at 45-94 months. Four peritoneal cases were treated with cytoreductive surgery and heated intraperitoneal chemotherapy and had not recurred at 6-36 months. The fifth patient with a peritoneal lesion was alive at 24 months without treatment. MTAP was assessed in 5 peritoneal cases and was retained in all of them.

Discussion: Rather than being localized, the lesions in this series diffusely involved the pleural or peritoneal surface, which the authors suggest may be a useful feature in the separation from WDPMT. The authors suggest that any lesion that has the histologic appearance of WDPMT should be subjected to BAP1 to look for loss of expression. All of the lesions in this series were associated with synchronous or metachronous invasive disease, but the course of disease was much more indolent that is typically seen in mesothelioma.

Take Home Message: In their discussion, the authors raise the question of how to separate mesothelial lesions that resemble WDPMT, but have BAP1 loss and “invasive foci” from diffuse invasive mesothelioma, as the surface component of some diffuse mesotheliomas mimics WDPMT. The crux of the matter is whether the designation of MIS mimicking WDPMT is appropriate for lesions that show any amount of invasion, as the WHO defines MIS as having no evidence of invasion. It would be interesting to know more about the existence and outcome of WDPMT-like lesions with BAP loss and no invasion.

Purpose: To assess the expression of GATA3 in primary lung carcinoma and correlate it with histologic subtype and expression of other commonly used immunomarkers.

Methods: Surgically resected primary NSCLCs from a single large U.S. academic medical center were retrospectively identified and TMAs were prepared. The TMA sections were stained with GATA3 (1:500, clone L50823; Biocare Medical), TTF-1 (clone 8G7G3/1), napsin A, and p40. GATA3-positive TMA cases were further analyzed with whole slide sections and staining was assessed semi-quantitatively for intensity (0-3+) and percentage of tumor cells staining. GATA3 staining was then categorized as negative (0-1+, <10%), low (1+, ≥10%), or high (any % 2 or 3+).

Results: Among 184 cases, 60% were adenocarcinoma (AdC), 27% squamous cell carcinoma (SqCC), 6% adenosquamous carcinoma (AdSqCC), 4% large cell carcinoma (LCC), 2% large cell neuroendocrine carcinoma (LCNEC), and 1% sarcomatoid carcinoma (SC). The overall frequency of GATA3 staining was 9%, which included 7/49 (14%) SqCC, 4/111 (4%) AdC, 2/11 AdSqCC, 2/7 LCC, and 1/2 SC (see Table 1). Four of the GATA3-positive SqCCs were keratinizing and 3 were non-keratinizing. The GATA3-positive AdCs included 2 acinar-predominant, 1 lepidic-predominant, and 1 solid-predominant (see Table 2). Only the squamous component stained in the GATA-positive AdSqCCs. Most of the GATA3-positive SqCCs (5/7) showed high expression, while the only AdC that did was solid-predominant. The GATA3 high expression SqCCs were also positive for p40 and negative for TTF-1 and napsin A. With the exception of the squamous component in AdSqCC, the GATA3 high expression non-SqCCs were all negative for p40, TTF-1, and napsin A. The GATA3 low expression AdCs were all positive for TTF-1 and/or napsin A and negative for p40.

Discussion: In this study, while 14% of SqCCs expressed GATA3, they all also expressed p40, a finding which is helpful in separating them from breast carcinoma. While most breast carcinomas are positive for GATA3, they are usually negative for p40. Urothelial carcinoma also typically expresses GATA3, but can also express p40, which makes distinguishing them from primary lung SqCC more difficult. CK7 and CK20 are reported to be more frequently expressed in urothelial carcinoma than lung SqCC, which may aid in the distinction.

While a few (4%) AdCs in this study were positive for GATA3, expression was low and was accompanied by TTF-1 and/or napsin A expression in most (3 of 4). The 4 NSCLCs in this study that were negative for TTF-1, napsin A, and p40 and showed low expression of GATA3 were potentially problematic, as these staining results could lead to a misdiagnosis of metastatic breast carcinoma. However, all of these cases were negative for other breast specific markers (e.g., ER, mammaglobin).

Take Home Message: High expression of GATA3 in a tumor in the lung does not necessary equate to metastatic breast or urothelial carcinoma, as occasional primary lung carcinomas can be positive for GATA3 and negative for TTF-1/napsin A. Don’t reply on GATA3 alone and expand the panel to include p40 and other site-specific markers.

Purpose: To systematically evaluate how unexpected molecular results from next-generation sequencing (NGS) in clinically suspected NSCLC aids diagnosis.

Methods: Cases in which NGS (OncoPanel version 3) had been performed on a malignant neoplasm clinically suspected to be NSCLC were retrospectively identified at a major academic U.S. medical center over a 39-month period.

Results: Cancer panel NGS results, along the clinicopathologic findings, were reviewed from 1007 consecutive patients. Based on the detection of an UV-radiation-associated mutational signature (n=6), gene fusions (n=2), and mutations (n=4), twelve (1.2%) patients had a final integrative diagnosis of cancer of extrapulmonary origin (see Table). The integrative diagnoses were cutaneous basal cell carcinoma (n=2), cutaneous squamous cell carcinoma (n=3), melanoma (n=1), metastatic thyroid carcinoma (n=1), synovial sarcoma (n=1), metastatic urethelial carcinoma (n=1), metastatic hepatocellular carcinoma (n=1), metastatic pancreatic adenocarcinoma (n=1), metastatic cholangiocarcinoma (n=1). Among the patients with revised diagnoses based on the integrated molecular results, 9 had multifocal disease and 10 had a history of prior malignancy. The anatomic pathology report had raised the possibility of non-pulmonary cancer in 5 of these cases.

Discussion: A small, non-negligible proportion of cases clinically suspected to be primary lung cancer are determined to be of extrapulmonary origin following NGS testing, most frequently arising from a cutaneous site.

Take Home Message: Although usually indolent, think of metastatic cancers of cutaneous origin, particularly when there is squamous or basaloid morphology and/or a history of skin cancer, and have a low threshold for NGS, as it may help clarify the diagnosis.

II. Articles for Notation

Original Articles – Neoplastic


Purpose: Identify germline pathogenic variants that are potentially actionable targets in mesothelioma.

Methods: Whole exome or whole genome sequencing was performed on 44 patients with mesothelioma.

Results: Pathogenic or likely pathologic variants in cancer-associated genes were found in 36% of patients. These including genes involved in DNA repair pathways (75%), as well as nucleotide excision repair, cell cycle regulation, base excision repair, and the hypoxic pathway. Almost one-third of mesothelioma patients with germline pathogenic variants also had a 1st or 2nd degree relative with mesothelioma, whereas none of the patients lacking a germline pathogenic variant...
did. Potential actionable targets were found in 9% of patients. Germline pathogenic variants were detected in two genes (\textit{NBN} and \textit{RAD51B}) that had not been previously associated with mesothelioma.

Take Home Message: Given the frequency of germline pathogenic variants in mesothelioma, it seems the time may be coming to consider routine germline testing of mesothelioma patients, as it has the potential to identify actionable targets and families who could benefit from genetic counseling and surveillance.

Centonze G, et al. Ascl1 and OTP tumour expressions are associated with disease-free survival in lung atypical carcinoids. Histopathology 2023;82:870-884

\textbf{Purpose:} To identify novel predictive factors in atypical carcinoid. Ascl1 is a regulator of genes involved in cell cycle progression. Earlier studies have shown it is expressed in carcinoids with the worst patient outcomes. OTP is a transcription factor that is expressed nearly exclusively in lung carcinoids and not in neuroendocrine tumors of other organs or high grade lung neuroendocrine carcinoma.

\textbf{Methods:} The immunohistochemical staining properties of a series of surgically resected atypical carcinoids were correlated with survival data.

\textbf{Results:} Of 58 atypical carcinoids, those that were Ascl1-positive, OTP-negative, and Ki-67 $\geq 10$ had a significantly worse prognosis than those with the converse immunoprofile (check out Figure 2 of the paper).

\textbf{Take Home Message:} Ascl1 and OTP, along with Ki-67, may become additions to the routine diagnostic evaluation of atypical carcinoid.

Fassi E, et al. Clinical presentation and outcome of patients with enteric-type adenocarcinoma of the lung: a pooled analysis of published cases. Lung Cancer 2023;179:107176

\textbf{Purpose:} To provide additional clinicopathologic information on enteric-type lung adenocarcinoma.

\textbf{Methods:} A systemic review of the published literature with inclusion of one additional previously unpublished case.

\textbf{Results:} Among 127 patients, median overall survival was 56 months and 14 months in early and advanced/metastatic-stage, respectively. Smoking and nodal involvement were independent adverse prognostic factors. Genetic alterations were relatively frequent with KRAS and NRAS being most common (31%), following by ROS1 (15%), RET (13%), BRAF (11%), EGFR (8%), and ALK (6%). DNA mismatch repair deficiency was seen in 15% of cases.

\textbf{Take Home Message:} While mismatch repair is rare in conventional lung adenocarcinoma (<1%), the frequency in enteric-type lung adenocarcinoma mirrors that of colorectal
adenocarcinoma. Data from this pooled analysis suggest a significant proportion of patients with enteric-type lung adenocarcinoma could benefit from targeted and/or immune checkpoint inhibitor therapies and should undergo molecular profiling.

**Handa T, et al. Comparison of ASCL1, NEUROD1, and POU2F3 expression in surgically resected specimens, paired tissue microarrays, and lymph node metastases in small cell lung carcinoma. Histopathology 2023;82:860-869**

**Purpose:** Determine extent to which intratumoral heterogeneity of various transcription factors results in discrepancies in expression between tissue sample types in small cell lung carcinoma (SCLC).

**Methods:** Immunohistochemical staining for ASCL1, NEUROD1, and POU2F3 was compared between whole slides of surgical samples, matched tissue microarray (TMA) cores that served as a surrogate for small tissue specimens, and lymph node metastases of SCLC. An H-score (% positive tumor cells x staining intensity on 0-3 scale) of >50 was considered positive.

**Results:** Of 77 cases, 52% showed an ASCL1-dominant staining pattern, 26% were NEUROD1-dominant, 20% were double-negative for ASCL1 and NEUROD1 with POU2F3 expression, and 3% were negative for all three markers in the surgical specimen. There was significant correlation between the surgical specimen immunoexpression pattern and that of their corresponding TMA core and lymph node metastasis.

**Take Home Message:** Biopsy and lymph node metastasis specimens, which are often the only specimens procured in SCLC patients, can be reliably used for subtyping defined by the immunoeexpression of ASCL1, NEUROD1, and POU2F3 markers.


**Purpose:** To understand the relationship between ciliated muconodular papillary tumor/bronchiolar adenoma (CMPT/BA) and lung carcinoma.

**Methods:** Cases of co-existing primary lung carcinoma and CMPT/BA from a single large cancer hospital in Japan were collected retrospectively and their clinicopathological findings and mutational profiles using target/whole exome sequencing were analyzed.

**Results:** From a study population of 1945 resected stage 0-III lung carcinomas, 8 cases (0.4%) with co-existing CMPT/BA were identified. All were male with a median age of 72 years and three-quarters were smokers. Five patients had adenocarcinoma (three had multiple adenocarcinoma), two had squamous cell carcinoma, and one had small cell carcinoma. No shared mutations between CMPT/BA and lung carcinoma were detected. **BRAF** (V600E) was the most frequent mutation in CMPT/BA, but a specific trend was not seen in driver mutations among the lung carcinomas.
Take Home Message: In the rare case of co-existing CMPT/BA and lung carcinoma, the lesions likely arise independently of one another.


Purpose: To determine whether the presence of micropapillary, solid, or both patterns in lymph node metastases is of prognostic value.

Methods: Survival data from patients with stages II to III lung adenocarcinoma who underwent lobectomy with lymph node dissection at a single large cancer hospital in the northeast U.S. were analyzed.

Results: Micropapillary and solid pattern in lymph nodes were associated with shortened overall 5-year survival (40% versus 63% for patients with neither of these patterns in lymph nodes).

Take Home Message: The presence of high grade (solid, micropapillary) histologic patterns in lymph node metastases strongly impacts survival. As it provides more prognostically useful information than the current pN classification, recording the histologic pattern of metastases may soon be coming to a synoptic report near you.

Original Articles – Non-neoplastic


Purpose: To improve understanding of genetic factors predisposing to familial pulmonary fibrosis (FPF), which is estimated to account for up to 20% of all cases of idiopathic interstitial lung disease.

Methods: Whole-exome and/or candidate gene sequencing from affected individuals was performed in a large cohort of FPF kindreds.

Results: Evaluation for rare genetic variants performed in 569 individuals showed that 14.9-23.4% of genetic risk in kindreds was explained by rare variants in genes, predominantly telomere-related, already linked to FPF. New candidate genes (SYDE1, SERPINB8, GPR87, NETO1) were identified in several families. The newly identified genes were not shared across multiple kindreds.

Take Home Message: A variety of genetic pathways mediate disease risk in the majority of FPF cases.

**Purpose:** Congenital pulmonary airway malformations (CPAMs) have traditionally been classified in types 0-4 according to the location in the airway tree from which they are thought to arise (Stocker classification). However, type 0 has been redesignated acinar dysplasia, while type 4 has come to be recognized as a DICER1 mutation-associated cystic form of pleuropulmonary blastoma. Recent evidence indicates that all type 1 and most type 3 CPAMs have mosaic KRAS codon 12 mutations, whereas type 2 CPAMs are likely related to bronchial atresia. This study seeks to determine whether there are indeed two distinct mechanisms that account for most CPAMs: 1) secondary to KRAS mosaicism, 2) due to bronchial atresia.

**Methods:** Congenital cystic lung lesions from a major children’s hospital were identified and KRAS exon 2 sequencing was performed on those with prominent cystic change that had been resected in early infancy.

**Results:** In contrast to 89 types 1 and 3 CPAMs (combined 91% KRAS mutation rate), all 23 type 2 CPAMs, as well as 11 intralobar and 10 extralobar bronchopulmonary sequestrations, and 10 bronchogenic cysts were wild-type for KRAS exon 2. Histologically, type 2 CPAMs and sequestrations frequently featured mucostasis and simple round cysts with flat epithelium, whereas types 1 and 3 CPAMs showed cystic architectural and epithelial complexity and mucostasis was rare.

**Discussion:** The histologic similarities and lack of KRAS mutation between sequestrations and type 2 CPAMs supports the hypothesis that type 2 CPAMs are related to bronchial obstruction. KRAS mutations appear to be an independent mechanism by which a subset of congenital cystic lung lesions develop.

**Review Articles**


A review of the facets of pulmonary hypertensive pathobiology with a nice schematic (Figure 1).


A comprehensive review of biomarkers as predictors of NSCLC response to immune checkpoint molecules.

**Case Reports**


A case of Vacuoles, E1 enzyme, X-linked Autoinflammatory, Somatic (VEXAS) syndrome with one of our journal club members (Dr. Yi) as a co-author. VATS biopsy showed wild-type
transthyretin amyloid deposition, which was likely incidental and not directly related to the patient’s VEXAS syndrome, which is a recently described systemic autoinflammatory disease with hematologic manifestations. About one-third to two-thirds of patients have respiratory manifestations that are non-specific. Lung biopsy findings that have been reported include organizing pneumonia and vasculitis.