PULMONARY PATHOLOGY JOURNAL CLUB
(May 2021 Articles)

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Table of Contents

Articles for Discussion

1. Thoracic nuclear protein in testis (NUT) carcinoma: expanded pathological spectrum with expression of thyroid transcription factor-1 and neuroendocrine markers. Hung YP, Chen AL, Taylor MS, et al. Histopathology 2021; 78:896-904.

2. Sialadenoma papilliferum of the bronchus: An unrecognized bronchial counterpart of the salivary gland tumor with frequent BRAF v600E mutations. Nakaguro M, Mino-Kenudson M, Urano M, et al. Am J Surg Pathol 2021; 45:662-671.

3. Cryobiopsy for identification of usual interstitial pneumonia and other interstitial lung disease features: Further lessons from COLDICE, a prospective multicenter clinical trial. Cooper WA, Mahar A, Myers JL, et al. Am J Respir Crit Care Med 2021; 203:1306-1313.

4. A postmortem portrait of the coronavirus disease 2019 (COVID-19) pandemic: A large multi-institutional autopsy survey study. Hooper JE, Padera RF, Dolhnikoff, M et al. Arch Pathol Lab Med 2021;145:529-535.

Articles for notation

Neoplastic lung disease

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2. PD-L1 immunohistochemistry in no-small-cell lung cancer: unraveling differences in staining concordance and interpretation. Keppens C, Dequeker EMC, Pauwels P, et al. Virchows Archive 2021; 478:827-839.

3. Recognition of filigree pattern expands the concept of micropapillary subtype in patients with surgically resected lung adenocarcinoma. Zhu E, Xie H, Gu C, et al. Modern Pathology 2021; 34:883-894

4. Novel histologic classification of small tumor cell nests for lung adenocarcinoma with prognostic and etiological significance: Small solid nests and pure micropapillary nest. Raito R, Ninomiya H, Okumura S, et al. Am J Surg Pathol 2021; 45:604-615.

Non-neoplastic lung disease

1. Family history of pulmonary fibrosis predicts worse survival in patients with interstitial lung disease. Cutting CC, Bowman WS, Dao N, et al. Chest 2021; 159:1913-1921.

2. Risk of primary graft dysfunction following lung transplantation in selected adults with connective tissue disease-associated interstitial lung disease. Natalini JG, Diamond JM, Porteous MK, et al. Journal of Heart and Lung Transplantation 2021; 40:351-358

3. Postmortem findings associated with SARS-CoV-2: Systematic review and meta-analysis. Satturwar S, Fowlkes M, Farver C, et al. Am J Surg Pathol 2021; 45:587-603.

4. Native lung complications after living-donor lobar lung transplantation. Mineura K, Chen-Yoshikawa TF, Tanaka S., et al. Journal of Heart and Lung Transplantation 2021;40-343-350.

5. Deceased-donor lobar lung transplant: A successful strategy for small-sized recipients. Campo-Canaveral De La Cruz, JL, Dunne B, Lemaitre, P, et al. J of Thor Cardiov Surg 2021; 161:1674-1685.

Case Reports

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2. Bilateral cystic bronchiectasis as novel phenotype of Niemann-Pick Disease Type successfully treated with double lung transplantation.
   B Tirelli C, Arbustini E., Meloni F. Chest 2021;159: e293-297.

3. Myopericytoma arising from myopericytosis—a hitherto unrecognized entity within the lung. Gruber-Moesenbacher U, Morresi-Hauff A, Behr K, et al.
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4. NUT midline carcinomas and their differentials by a single molecular profiling method: a new promising diagnostic strategy illustrated by a case report. Haefliger S, Tzankov A, Frank S, Bihl M, Vallejo A, Stebler J, Hench J.
   Virchow Archive 2021; 478:10007-1012.

Editorials

1. Expanding the utility of cytology preparations in cancer biomarker testing. Sholl LM, Hwang DH. Cancer Cytopathology 2021;337-340.

2. Lung cancer in Austria. Pirker R, Prosch H, Popper JH, et al. Journal of Thoracic Oncology 2021; 16:725-733.

Letters

1. Cannabis use and lung cancer: time to stop overlooking he problem? Betser L, Glorion M, Mordant Pl, et al. Eur Respir J 2021; 57:2004132

Review Articles

1. Molecules in pathogenesis: Angiotensin converting enzyme 2 (ACE2). Wiese L, Zemlin AE, Pillay TS. J Clin Pathol 2021; 74:285-290.

2. SWI/SNF-deficient thoraco-pulmonary neoplasms. Sesboue C, Loarer FL. Seminars in Diagnostic Pathology 2021; 38:183-194.

3. Two sides of the same coin? A review of the similarities and differences between idiopathic pulmonary fibrosis and rheumatoid arthritis-associated interstitial lung disease. Matson S, Lee J, Eickelberg O. Eur Respir J 2021; 57:2002533

Articles for Discussion

1. Thoracic nuclear protein in testis (NUT) carcinoma: expanded pathological spectrum with expression of thyroid transcription factor-1 and neuroendocrine markers.
Hung, YP, Chen AL, Taylor MS, Huynh, TG, Kem M, Selig MK, Nielsen GP, Lennerz JK, Azzoli CG, Dagog-Jack I, Kradin RL, Mino-Kenudson M.
Histopathology 2021; 78:896-904.

Background: NUT carcinoma is an aggressive malignancy driven by NUTM1 rearrangements and classically shows squamous differentiation with abrupt keratinization. This study was inspired by an index case that showed diffuse TTF-1 expression and was initially diagnosed as pulmonary adenocarcinoma.

Purpose: To determine how often NUT carcinomas are not recognized initially, and to describe the spectrum of morphology and immunophenotype.

Methods:

- Retrospective review of surgical pathology files at MGH (2012-2019)
- Searched for NUTM1 rearrangements in 2289 consecutive primary thoracic tumors analyzed with RNA-based fusion sequencing assays (2013-2019)
- Performed NUT immunohistochemistry on tissue microarrays with 425 additional primary lung adenocarcinomas (2000–2006 and 2008–2015)

Results:

- Identified 6 patients with thoracic NUT carcinomas (confirmed by molecular testing)
    - 5 men and 1 woman; 4 never-smokers; median age 58 years (31–80 years); median death 2.8 months (2.3–12.9 months) **[Table 1]**
    - Index case had predominantly pleural disease, 5 had bulky central disease

- 2 cases identified by histopathology and 4 by molecular testing, including index case (initial dx: metastatic adenocarcinoma, SCC with basaloid features, poorly differentiated carcinoma, non-small-cell carcinoma)
    - NUTM1 rearrangements accounted for 0.23% (5/2216) of all primary thoracic malignancies tested
    - No additional cases found by IHC screening
- Histologically, all tumors were primitive-appearing, focal keratinization in 4
- Immunohistochemistry showed diffuse speckled nuclear staining of NUT (5/5), positive TTF-1 (1/6, index case), p40 (3/4), CK5/6 (3/4), cytokeratin MNF116 (5/5), synaptophysin (2/6), chromogranin (1/6), and patchy/rare INSM1 (2/2). Napsin A was negative (0/3) **[Table 2]**

Take Home Messages:

- Diagnosis remains challenging (4/6 diagnosed by molecular weeks-months later).
- NUT carcinoma can occasionally express TTF-1 and/or multiple neuroendocrine markers, a diagnostic pitfall to be aware of.
- NUT immunohistochemistry and/or molecular testing should be considered in primitive-appearing tumors, regardless of immunophenotype.
- Clinical relevance: selective bromodomain inhibitors are under clinical investigation.

2. Sialadenoma papilliferum of the bronchus: An unrecognized bronchial counterpart of the salivary gland tumor with frequent BRAF v600E mutations.

Nakaguro M, Mino-Kenudson M, Urano M, Ogawa I, Honda Y, Hirai H, Tanigawa M, Sukeda A, Kajiwara N, Ohira T, Ikeda N, Mikama Y, Tada Y, Ikeda J-I, Matsubayashi J, Faquin WC, Sadow PM, Nagao T.
Am J Surg Pathol 2021; 45:662-671.

Background: Primary tracheobronchcial tumors of the lung are uncommon, but the vast majority of them are malignant. Benign neoplasms in this area are rare, but given the crucial patient management differences between malignant and benign variants, clarity regarding this difficult pathologic differential diagnosis is essential. Salivary gland-type tumors that arise from the bronchial glands most commonly are adenoid cystic and mucoepidermoid carcinomas. However, more rare malignant and benign variants including epithelial-myoepithelial carcinoma, pleomorphic adenoma, and sialadenoma papilliferum (SP) have been reported.

- Sialadenoma papilliferum (SP) is rare and benign and thought to arise within the excretory duct of these glands.

- This tumor has histologic features of both surface exophytic papillary proliferations and deep, multicystic intraductal papillary epithelial components and can be mistaken for a malignancy.
- Three cases in the bronchus have been reported, but are difficult to confirm given the necessity of evaluating the cellular and architectural components of both the exophytic and intraductal components. *BRAF* V600E mutations have been reported in salivary gland SP cases.

Purpose: This study reports the clinical, pathologic, immunohistochemical, and molecular features of 4 cases of SP arising in the bronchus and discusses the diagnostic pitfalls with glandular papillomas (GP) and mixed squamous cell and glandular papillomas (MP). Further, BRAF V600E mutations are evaluated by mutational analysis and specific immunohistochemistry in these 4 lesions.

Methods:

- A retrospective search of the pathologic archives of the departments of pathology at Nogoya University School of Medicine, Fujita Health University, Hiroshima University, Kumamoto University and Tokyo Medical University recovered 4 cases that were histologically confirmed by five expert pathologists.
- Hematoxylin and eosin, PAS, mucicarmine and IHC for BRAF V600E and TTF-1 were performed. Mutational analysis by PCR and Sanger sequencing on formalin-fixed paraffin embedded tissue were performed for key oncogenes (*BRAF*, *PIK3CA*, *HRAS* and *KRAS*.)

Results:

- Age range: 52-77; 2M, 2F;
- Pre-operative biopsy diagnoses in 3 of the 4 lesions suspected atypical or malignant tumors.
- One of the 4 tumors on resection specimen was called an adenocarcinoma and one was diagnosed as squamous cell carcinoma in situ, both leading to resections.
- P63-postive basal cells are present in the exophytic papillary epithelium and multicystic component; SMA is negative.
- TTF-1 is negative throughout
- BRAF V600E IHC is positive in inner ductal epithelial cells.

Take Home Messages:

- SP is a benign tumor but several histomorphologic features may cause confusion with malignancy on biopsy specimens.

    - Complex architecture of the epithelial tufts can mimic micropapillary Adenoca.
        - One (1) case was diagnosed as adenocarcinoma on biopsy.
    - Nuclear features have mild to moderate atypia with rare mitoses raising possible squamous cell carcinoma (SCC) in situ dx.
        - One (1) case classified as SCC in situ on biopsy
- P63 confirms intraductal basal cell rimming.
- + *BRAF* V600 E mutations are seen in 50% of cases

2. **Cryobiopsy for Identification of usual interstitial pneumonia and other interstitial lung disease features: Further lessons from COLDICE, a prospective multicenter clinical trial.**

Cooper WA, Mahar A, Myers JL, Grainge C., Corte TJ, Williamson JP, Vallely MP, Lai S, Mulyadi E, Torzillo PJ, Phillips MJ, Lau EMT, Raghu G, Troy LK.
Am J Respir Crit Care Med 2021; 203:1306-1313.

Background: Transbronchial lung cryobiopsy (TBLC) is a new technology for interstitial lung disease diagnosis. The reported histopathologic diagnostic yield for TBLC is approximately 80%. The impact of TLBC on multidisciplinary discussion diagnosis (MDD) compares favorably with surgical lung biopsy (SLB). There is good histopathologic agreement between TBLC and SLB. However, because of the smaller size and the location of the tissue taken during a TBLC (i.e., centrilobular location with UIP a predominantly peripheral process), the diagnostic confidence was frequently lower for TBLC than SLB.

Purpose: The purpose of this study is to define the specific histopathologic features of TBLC that predict a diagnosis of usual interstitial pneumonia (UIP) in a corresponding SLB and to define the clinical indices that predict biopsy concordance between TBLC and SLB for a UIP diagnosis.

Methods:

- The Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease Alliance (COLDICE) was a prospective, multicenter study investigating the diagnostic agreement between TBLC and SLB.
- The participants underwent both procedures with pathologists blinded to the type of biopsy procedure.
- The pathologists applied the international guideline criteria (American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association IPF guidelines).

- Using the results from 65 patients from the COLDICE study, the TBLC histopathologic, clinical, radiologic, and procedural features predictive of UIP in the paired SLB and of overall concordance were analyzed.

Results:

- UIP was identified in 33/65 SLB and 81.5% were concordant with the TBLC.
- The most frequently reported UIP guideline criteria in TBLCs were 'patchy fibrosis' (100%), 'fibroblast foci' (87.9%) and the 'absence of alternative diagnostic features' (90.9%) and these three features strongly predicted histopathologic concordance with a diagnosis of UIP on the SLB.
- The UIP guideline criteria of 'predominantly subpleural or paraseptal fibrosis' was infrequently report (24.2%).
- Increased numbers of TBLC samples predicted histopathologic concordance with SLB.
- Fibrotic HP was the most frequent second choice for the pathologic dx.
- Clinical features of discordance included older age, family history of ILD, and radiologic asymmetry.

Take Home Messages:

- Subpleural and/or paraseptal fibrosis were not essential for the diagnosis of UIP in TBLC if 'patchy fibrosis', 'fibroblast foci' and 'absence of alternative diagnostic features' were present.
- The more samples taken during the TBLC, the higher the diagnostic accuracy.
- The 2018 UIP histopathology guidelines may need refinement for specific application to TBLC specimens.
-

3. A postmortem portrait of the coronavirus disease 2019 (COVID-19) pandemic: A large multi-institutional autopsy survey study.

Hooper JE, Padera RF, Dolhnikoff, M, da Silva, LFF, Duarte-Neto, AM, Kapp ME, Lacy JM, Mauad T, Saldiva PHN, Rapkiewicz AV, Wolf DA, Felix JC, Benson P, Shanes E, Gawelek KL, Marshall DA, McDonald MM, Muller W, Priemer DS, Solomon IH, Zak T, Bhattacharjee MK, Fu L, Gilbert AR, Harper HL, Litovsky S, Lomasney J, Mount SL, Reilly S, Sekulic M, Steffensen TS, Threlkeld KJ, Zhao B, Williamson AK.

Arch Pathol Lab Med 2021; 145:529-535.

Background: SARS-CoV-2 emerged in the United States in 2019 and has since created a global pandemic. The spectrum of disease causes by SARS-CoV-2 infection in humans (coronavirus disease 2019-COVID-19) includes pulmonary, cerebral, myocardial, hepatic, and renal pathology

and clotting dysfunction. Most pathology studies report findings from relatively small and homogenous patient populations, and many are limited in their scope of evaluation (number of organs examined and biopsy, resection or postmortem samples).

Purpose: The purpose of this study is to compile the largest demographic, clinical, and postmortem data in those dying of or with COVID-19 to date.

Methods:

- The study draws from a diverse patient population and the combined experience of numerous pathologists from across the United States and in Sao Paolo, Brazil.
- Pathologists were invited to contribute by written invitation to all participants on the 'COVID Autopsy Listserve'
- Comprehensive data from 135 postmortem evaluations of COVID-19 including histologic evaluation of all organ systems in most cases is provided via a 49-question survey. **(Table 1-5)**
- A positive diagnosis of COVID-19 was done by PCR on antemortem (110) or postmortem (12), nasopharyngeal swabs (5) postmortem tracheal and lung swabs (1) or a combination of these methods (5).
- Postmortem evaluations were conducted by a) biopsy samples of lungs, liver, heart, kidneys spleen, brain skin, skeletal muscle and testis (36) and at least in situ evaluation of body cavities and organs (99).

Results:

- 135 cases had the following demographics when compared to the overall US COVID statistical mode
    - Younger
    - More male
    - More Black or African American, and less Hispanic
    - Same proportionality of White and Asian ethnicities
- Preexisting diseases
    - All had more than 1 preexisting disease (PED) with average PED of 2.88
        - Systemic hypertension: 64%
        - Diabetes mellitus: 52%
        - Obesity: 34%
        - Coronary artery disease (25%)
- Clinical conditions during hospitalization
    - 113/135 (84%)---acute respiratory disease
    - 73/135 (54%)---acute kidney dysfunction

- 47/135 (35%)---acute myocardial dysfunction
- 46/135 (34%)---disseminated intravascular coagulation
- 14/135 (10%)---concurrent infections

(See Table 1).

- Pulmonary pathology
  - DAD, acute---75%
  - DAD, organizing---47%
  - Hemorrhage---43%
  - Acute bronchopneumonia---41%
    - Most attributed to superinfection
  - Tracheitis/bronchitis/bronchiolitis---30%
  - Mucus in airways---16%
  - Emphysema---10%
  - Edema or vasculitis---5%
  - Not identified/assessed 2%
  - Thrombosis in lungs---Macroscopic: 16%
    Microscopic: 39%
  - Prominent cellular inflammatory response in tissue or in vasculature of the lungs was not seen.

(See Table 2).

- Cause of Death
  - Acute respiratory disease---75%
  - Acute myocardial infarction---4%
    - The pathologic finding of myocarditis---6%

Take Home Messages:

- The largest autopsy study of COVID-19 patients from the United States and Brazil revealed acute respiratory distress syndrome (ARDS) as the major cause of death and acute or organizing DAD as the major pathology in the lungs
- Assumptions about disease, such as the apparent ubiquity of widespread cellular inflammatory processes in the organs throughout the body including the lungs and heart (myocarditis) were not substantiated.
- Given the certainty of deaths from novel infectious diseases in the years to come, pathologists trained and willing to perform detailed postmortem analysis should be supported to gain the most knowledge of these new diseases.

Articles for notation

Neoplastic lung disease

1. **Prospective multicenter validation of the detection of ALK rearrangements of circulating tumor cells for non-invasive longitudinal management of patients with advanced NSCLC.** Ilie M, Mazieres J, Chamorey E, et al.
   Journal of Thoracic Oncology 2021; 16:807-816
   Summary: A multicenter, prospective observational study for 203 patients with stage IIIB NSCLC in 9 French centers, 81 of which with *ALK* positive and 122 *ALK* negative tumors. Blood samples collected at 0, 6 and 12 weeks were collected. *ALK* gene rearrangements were evaluated in CTCs using IHC and FISH. There was a high concordance between detection of ALK rearrangements in tumor tissue and in CTCs by IHC (94.4% sensitivity;89.4% specificity).
   Take home message: This represents the first CTC-based *ALK* rearrangement assay validated with clinical samples. CTCs may be a complementary tool to a tissue biopsy for the detection of ALK rearrangements, but longer post-therapy time periods need to be studied.

2. **PD-L1 immunohistochemistry in non-small-cell lung cancer: unraveling differences in staining concordance and interpretation.**
   Keppens Cl, Dequeker EMC, Pauwel P, i.et al.
   Virchows Archive 2021; 478:827-839.
   Summary: Staining quality and estimation of tumor proportion score (TPS) in NSCLC by European Society of Pathology. Stained microarrays from throughout Europe were reviewed by three experts and scored (expert staining score-ESS). ESS was correlated with a variety of protocols.
   Take home message: 32 different combinations of primary antibodies (predominantly three antibodies: 22C3, SP263, E1L3N), antigen retrieval, and detection methods. There is considerable variability in protocols, laboratories 'characteristics, LDTs versus kits, and incidence of reporting an incorrect TPS. A lot of data to get through reveals some good lessons (i.e., reading the directions on the antibody kits helps.)

3. **Recognition of filigree pattern expands the concept of micropapillary subtype in patients with surgically resected lung adenocarcinoma.**
   Zhu E, Xie H, Gu C, et al.
   Modern Pathology 2021; 34:883-894
   Background: Numerous studies have demonstrated that the micropapillary pattern (MP) of adenocarcinomas is associated with worse survival outcomes, a higher risk of disease recurrence and survival benefits from adjuvant chemotherapy, even with only small amounts of this pattern present. A recently added filigree pattern has been found to be associated with MP and similar clinical and survival outcomes have been seen in these two patterns, raising the possibility that the filigree pattern is a type of MP.

   Purpose: This study investigates the clinicopathologic characteristics and prognostic significance of the filigree pattern of adenocarcinomas and attempts to clarify/validate the relationship between the filigree pattern and classical micropapillary adenocarcinomas.

   Methods: A large study (n=461); cases were from a total of 1123 lung cancer resections at Shanghai Pulmonary Hospital with inclusions criteria of adenocarcinoma, single lesion with complete resections and no neoadjuvant therapy. Outcomes were tumor recurrence diagnosed by clinical, radiological, or pathological data and survival by outpatient clinic visits. Two pathologists evaluated tumor slides. Lymph nodes slides were stained with cytokeratin IHC to evaluate for the presence of micro metastases. The presence of absence of MP, filigree or both was recorded with a number of other pathologic features (other invasive patterns present and predominant pattern present; STAS, pathologic stage, etc.).

   Results: Filigree pattern was present in 32% and was more likely to be seen in larger and higher stage tumors, and with STAS. The presence of the filigree pattern was highly associated with MP. Multivariate analysis revealed that the presence of MP and/or filigree pattern was an independent prognostic factor and that recurrence free survival (RFS) was the worse for tumors with both MP and filigree than with only MP. The presence of any amount of filigree pattern was associated with poor survival and with the presence of lymph node micrometastases. Because both MP and the filigree pattern are associated with a similar poor prognosis and LN micrometastases and highly associated with MP, they are put into the same pattern.
   Take home message: MP and filigree pattern of MP have a worse prognosis when present in adenocarcinoma and have an increased incidence of LN micrometastases. No

matter what you call it, a careful evaluation of the LNs with IHC may be warranted in adenocarcinomas with MP pattern.

4. **Novel histologic classification of small tumor cell nests for lung adenocarcinoma with prognostic and etiological significance: Small solid nests and pure micropapillary nest.**
   Raito R, Ninomiya H, Okumura S, et al.
   Am J Surg Pathol 2021; 45:604-615.
   Summary: This study clarifies the implications of small tumor cell nests by introducing a new dichotomic classification based on the glandular polarity of tumor cells: pure micropapillary nests (pMPs), preserving glandular polarity, and small solid nests (SSNs), lacking polarity.
   Take home message: The diagrams were difficult to apply and interobserver variability may be high.

Non-neoplastic lung disease

1. **Family history of pulmonary fibrosis predicts worse survival in patients with interstitial lung disease.**
   Cutting CC, Bowman WS, Dao N, et al.
   Chest 2021; 159:1913-1921.
   Summary: Patients with a self-reported family history of ILD (IPF, CTD-associated ILD, CHP, and unclassifiable ILD) present with a unique phenotype regarding clinical characteristics and longitudinal outcomes when compared with their counterparts with sporadic disease.
   Take home message: Large study (1,262 patients: 58% with IPF and 42% with non-IPF) all with MDD. 17.7% of all patients reports family history; 25.1% of IPF and 12.4% of non-IPF ILD had family history. If you believe the patients' history of a family member with ILD, this study suggests a worse prognosis with a family history no matter what type of ILD they have. Genetic testing would be of interest to confirm and enhance these findings.

2. **Postmortem findings associated with SARS-CoV-2: Systematic review and meta-analysis.**
   Satturwar S, Fowlkes M, Farver C, et al.
   Am J Surg Pathol 2021; 45:587-603.
   Summary:

- A meta-analysis of autopsy findings based on data from articles on SARS-CoV-2 (COVID-19), (n=241 patients) and SARS-CoV-1 (n=91 patients)
- SARS-CoV-1 patients were younger (50 years mean age) than SARS-CoV-2 patients (70 years mean age).
- Initial clinical presentation in both cohorts was similar (respiratory sx).
- Pulmonary pathology findings in the majority of patients in both SARS-CoV-1 and SARS-CoV-2 was DAD.
    - Pulmonary thrombi were present in both groups, mostly in small peripheral vessels
    - Multi-nucleated giant cells were common in both, representing a mix of macrophages and pneumocytes
- DAD is the major cause of death in SARS-CoV-2 patients

Take home message: A literature comparison of SARS-CoV-1 and SARS-CoV-2 that revealed similarities in lung pathology (DAD), but with clinical differences and outcomes (age: SARS-CoV-1: 50 years; SARS-CoV-2: 70 years and death toll: SARS-CoV-1: 800 deaths; SARS-CoV-2: 3.8 million deaths).

3. **Risk of primary graft dysfunction following lung transplantation in selected adults with connective tissue disease-associated interstitial lung disease.**
   Natalini JG, Diamond JM, Porteous MK, et al.
   Journal of Heart and Lung Transplantation 2021; 40:351-358.
   Summary: Primary graft dysfunction (PGD) in patients transplanted for CTD-ILD vs IPF was evaluated in 101 CTD-ILD pts and 501 IPF pts. CTD-ILD pts had longer postoperative hospitalizations compared IPF patients, but no increased risk for PGD.
   Take home message: A large, well-done study in lung transplants in CTD-ILD patients, an area of increasing focus. Though longer hospitalizations when compared to non-CTD-ILD patients, they have similar outcomes and, in this case, no increased risk for PGD. Lung transplant is a potentially life-saving procedure in CTD-ILD pts, yet programs continue to be reluctant to transplant these patients, mostly because of long term non-pulmonary manifestations that may limit their outcomes.

4. **Deceased-donor lobar lung transplant: A successful strategy for small-sized recipients.**
   Campo-Canaveral De La Cruz, JP, Dunner B, Lemaitre, P, et al.
   J of Thor Cardio Surg 2021; 161:1674-1685.
   Summary: Lobar lung transplantations (LLtx) from deceased donors has been a potential solution for small sized recipients. A large (1665 pts--LLTx: 45%; LTx: 55%) study that shows these pts do as well as complete lung transplantation patients.

Take home message: A procedure long championed in Japan and slow to take hold in the US, this study may push this area forward in smaller recipients (young CF patients, etc.) and in centers with the technical expertise to perform them.

5. **Native lung complications after living-donor lobar lung transplantation.**
   Mineura K, Chen-Yoshikawa TF, Tanaka S., et al.
   Journal of Heart and Lung Transplantation 2021;40-343-350.
   Summary: A smaller Japanese study done with living donors, but also shows that LLTx have similar results to complete lung transplants, i.e., single lobes work as well as whole lungs.
   Take home message: Used in Japan for critically ill patients who cannot wait for complete lung transplant; a procedure that could gain momentum in the US if donor cadaveric lung become difficult to acquire.

Case Reports

1. **A well-defined endobronchial tumor in a 26-year-old man**.
   Triantaflyllidou C, Effraimidis P, Schimanke M, et al.
   Chest 2021;159:e313-317.
   Take home message: A primary pulmonary leiomyosarcoma presenting as asthma. They represent 0.5% of all primary lungs, but are the most common primary lung sarcoma. These sarcomas usually present in the parenchyma. The unusual clinical presentation in this patient of airway obstruction symptoms, was cause by this 4.0 cm predominantly parenchymal mass growing into the proximal airway (with a nice gross image to highlight this).

2. **Bilateral cystic bronchiectasis as novel phenotype of Niemann-Pick Disease Type B successfully treated with double lung transplantation.**
   Tirelli C., Arbustini E., Meloni F.
   Chest 2021; 159: e293-297.
   Take home message: An addition of bronchiectasis to the description of the pathology seen in the lungs of patients with Niemann-Pick Disease (Type B) that undergo transplantation with a nice summary table of clinical findings.

3. **Myopericytoma arising from myopericytosis—a hitherto unrecognized entity within the lung.**
   Gruber-Moesenbacher U., Morresi-Hauff A., Behr K., et al.
   Virchows Archive 2021; 478:841-849.

Take home message: A true case report----the first description of myopericytoma arising within myopericytosis with suggestions for future therapies (should this every be seen/recognized again!) using antiangiogenic therapies.

4. **NUT midline carcinomas and their differentials by a single molecular profiling method: a new promising diagnostic strategy illustrated by a case report.**
   Haefliger S, Tzankov A, Frank S, Bihl M, Vallejo A, Stebler J, Hench J.
   Virchow Archive 2021; 478:10007-1012.
   Take home message: It is increasing clear that molecular studies that look for chromosomal rearrangements in testis (NUT) gene (*NUTMI*) are needed for this diagnosis. Also, using standard DNA methylation array analysis based on data from the TCGA and GEO databases, the authors offer thoughts on the histogenesis of these tumors and details of the technology are published to encourage further exploration of NMCs in this regard.

Editorials

1. **Expanding the utility of cytology preparations in cancer biomarker testing.**
   Sholl LM, Hwang DH.
   Cancer Cytopathology 2021;337-340.
   Take home message: A recap of recent discoveries of a variety of genomic alterations in driver oncogenes with an eye on novel, specific inhibitors for first-line therapy for *RET, MET, NTRK, ROS1.* These build on prior approvals for first-line targeted therapies for *EGFR, BRAF,* and *ALK*. Techniques to diagnose these genomic alterations in NSCLC are reviewed and their potential use in tumors outside of the lung is discussed. Highlighting the use of cytology smears of neoplasms from a variety of organs, the authors focus on problems specific to cytologic preparations and encourage further innovations to optimize these specimens for use in biomarker testing.

2. **Lung cancer in Austria.**
   Pirker R., Prosch H., Popper JH., et al.
   Journal of Thoracic Oncology 2021; 16:725-733.
   Take home message: Lung cancer (LC) is a major health problem in Austria and the authors summarize the current status and outline strategies for decreasing the burden of LC in Austria with a review of tobacco control (smoking bans began in 2019 and are increasing), screening (just beginning), clinical and pathologic diagnostic algorithms, molecular testing and therapies. The overall audit was conducted by The Austrian

Society of Pneumonology. Beginning a National Cancer Registry and a National Audit is suggested.

Letters

1. **Cannabis use and lung cancer: time to stop overlooking the problem?**
   Betser L, Glorion M, Mordant Pl, et al. Eur Respir J 2021;57:2004132
   Take home message: A French study comparing cannabis plus tobacco smokers (CTS) with tobacco only smokers (TS) and nonsmokers (NS) reveals statistically significant differences as follows: 1) a younger population (44 years for CTS versus 47 years for TS and 45 years for NS), 2) a higher proportion of men, 3) a higher frequency of emphysema (91% for CTS versus 50% for TX and 11% for NS), 4) a higher % of large cell carcinomas, bigger tumors (T3 and T4) and upper lobe predominant. Average amount of smoking were 150 joints/month. The authors suggest these features may be secondary to the co-carcinogenic role of polycyclic hydrocarbons and tar particles in cannabis.

Review Articles

1. **SWI/SNF-deficient thoraco-pulmonary neoplasms.**
   Sesboue C, Loarer FL.
   Seminars in Diagnostic Pathology 2021; 38:183-194.
   Take home message: A comprehensive review of the clinical, histopathologic, immunophenotypic and molecular features of SMARCA4-deficient lung carcinomas and SARCA4-deficient undifferentiated thoracic tumors. Also, this comments on SMARCA4 deficiency in mesotheliomas and sarcomas associated with recurrent SMARCB1 inactivations.

2. **Molecules in pathogenesis: Angiotensin converting enzyme 2 (ACE2).**
   Wiese L, Zemlin AE, Pillay TS.
   J Clin Pathol 2021; 74:285-290.
   Take home message: A nicely illustrated review of this increasing important enzyme, expressed in alveolar epithelial cells, in the pathogenesis of the severe respiratory syndrome of SARS-CoV-2 and its role as a possible therapeutic target.

3. **Two sides of the same coin? A review of the similarities and differences between idiopathic pulmonary fibrosis and rheumatoid arthritis-associated interstitial lung disease.**

   Matson S, Lee J, Eickelberg O.

   Eur Respir J 2021; 57:2002533

   Take home message: A comprehensive review of the similarities and differences in the epidemiology, natural history, clinical characteristics, radiologic and histologic patterns in RA-ILD versus IPF. A look at the genetic susceptibility of both diseases focuses on the similar genetic mutations found in both diseases involving *TERT*, *RTEL1, PARN*, *SFTPC* and *MUC5.* The authors conclude with thoughts on what we can learn about IPF by studying RA-ILD.