

Journal Club
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Articles for Discussion

1. **Woge MJ, Ryu JH, Bartholmai BJ, Yi ES. Cicatricial organizing pneumonia: a clinicopathologic and radiologic study on a cohort diagnosed by surgical lung biopsy at a single institution. Hum Pathol. 2020;101:58-63.**

Background: We are all aware of the growing literature on cicatricial or fibrosing organizing OP (CiOP). Some studies have looked at cryptogenic cases (Yousem) while others have looked at CiCOP as a pattern (Churg). This current study analyzes CiOP as a pattern and compares those with <10% to those with >10%.

Methods: Files of Mayo Clinic Rochester were searched for OP or BOOP (2005-2013). Cases were excluded for a variety of reasons leaving a total of 56/659 cases.

- All cases evaluated for percent collagen deposition within Masson bodies, presence of linear fibrous bands mimicking fNSIP; and intraluminal/dendriiform ossification. Clinical and radiographic records were also reviewed.
- Although not clearly stated in the methods, the results make it clear that the authors then compared cases with $\geq 10\%$ cicatricial features to those with less than 10%. Not clear why 10% was chosen. They then do a deep dive into those with 50% (again no justification for this cut point).

Results:

Pathology :32/56 (57.1%) showed 10% cicatricial foci and 9 (16.1%) revealed cicatricial elements comprised of 50% or greater OP. Among those with $\geq 10\%$, 78% were COP, while the rest secondary. Among those with < 10%, 58% COP, rest secondary.

- All of the $\geq 50\%$ cases (9) showed linear fibrous bands and 5 of 9 showed intraluminal ossification.
- Some areas superficially mimicked fibroblast foci of UIP.

Clinical and Radiologic Features: Tables 1 and 2 give clinical and radiologic characteristics. Table 1 shows the entire group broken down by degree of cicatricial features (10% cut off).

- $\geq 10\%$: 27 men and 5 women, median 68 years (28-80 yrs). Secondary causes: CTD, including adult Still's, proximal airway obstruction due to tumor, myelodysplastic syndrome, and "others".
- Among both groups, 53 (94.6%) had one preop CT and 34 pts (60.7%) had follow-up CT ranging from 0.4 to 171 months. The overall clinical findings and both preoperative and postoperative radiologic features appeared similar in patients with and without CiOP features.
- The follow-up CT results show that only 10% of patients with OP greater than 10% cicatricial component did worse which was pretty similar to the 2/24 (14%) of patients with less than 10% cicatricial component.
- A similar number of patients were alive and doing well at last follow-up between the two groups.

Table 2 highlights 9 patients with greater than 50% CiOP: Among the 9 (7 men and 2 women) with 50% or more CiOP, 7 were cryptogenic, 1 had RA, and one aspiration. Interestingly, 6 of the 9 did not have any significant symptoms.

Discussion: Authors emphasize that in 16% of their cases when CiOP was present it was accompanied by linear fibrous bands reminiscent of UIP and some of which were also associated with ossification.

Many of the CiOP patients did not have significant respiratory symptoms. Among the patients with greater than 50% CiOP 6 of 9 were alive or stable and the cause of death in the remaining 3 were not related to CiOP.

- Authors briefly discuss the challenge of differentiating CiOP from fNSIP and UIP. Authors discount the idea that this represents a genuine COP fNSIP overlap.

Authors speculate on the difference between the results of this study and other studies of CiOP. Highlight the fact that they have one institution and looked at all comers with OP

Comment: Another study focusing on CiOP as a pattern. Design commendable, in that they look at all OP cases for a given time period. They do break out a small group with $\geq 10\%$ CiCOP that does not seem to do worse, similar to the findings of Churg (but not Yousem).

2. **Bilecz A, Stockhammer P, Theegarten D, Kern I, Jakopovic M, Samarzija M, Klikovits T, Hoda MA, Döme B, Oberndorfer F, Muellauer L, Fillinger J, Kovács I, Pirker C, Schuler M, Plönes T, Aigner C, Klepetko W, Berger W, Brcic L, Laszlo V, Hegedus B. Comparative analysis of prognostic histopathologic parameters in subtypes of epithelioid pleural mesothelioma. *Histopathol.* 2020;77:55-66.**

Background: This study attempts to determine the prognostic significance of architecture, cytology, mitotic activity and necrosis in epithelioid malignant mesotheliomas (eMPM).

Methods: Multicenter study from multiple Central European countries. 192 total patients (1994-2015). Samples: Training set: VATS, 106; needle core, 28; pleurectomy, 28; 30 cases not specified. Validation set: 55 digital images of eMPMs available from a Cancer Digital Slide Archive submitted by tissue source sites of The Cancer Genome Atlas (TCGA).

Design: One H&E section provided by participating centers classified by two of the authors: predominant growth pattern, presence of pleomorphic features (at least 10%). Tubulopapillary, solid, trabecular, microcystic, micropapillary, mitotic figures (hot spots at 400x/10 high-power fields). A necrosis mitosis score was calculated according to Rosen LE et al, (*Modern Pathol*, 2018;31:598-606). M/N (0-2) composite nuclear grade was calculated based on nuclear atypia and mitotic count. Features correlated with overall survival (OS) defined as time to diagnosis to date or death or last contact. Kaplan-Meier, multivariate Cox regression and other statistical analyses performed.

Results: Due to low number of micropapillary variants they were excluded from OS analysis.

Tubulopapillary and microcystic associated with better survival.

Solid and trabecular had shorter survivals.

Pleomorphic had shortest survival significantly worse than tubulopapillary, microcystic and solid and showed a trend towards worse outcome than predominant trabecular.

- Patients with tumors of M/N scores of 1, 2 and 3 had significantly different OS of 720 days, 386 days (P=0.0004) and 165 days (P=0.0036). No significant difference in OS between nuclear grades 1 and 2. Patients with nuclear grade 3 have significantly worse OS compared to patients with nuclear grade 2 (OS 486 versus 123), P=0.0002.
- The presence of necrosis was also associated with significantly shorter OS in compared to those without (281 versus 727), P <0.0001.

Validation cohort: the results in the validation cohort supported the results from the training set.

Impact of Morphologic Subtype in Multimodal Therapeutic (MMT) Setting

Among patients with MMT and tubulopapillary/microcystic patterns did better than solid/trabecular pattern tumors.

Among those not receiving MMT there was no significant difference between these two main groups.

Discussion: Authors point out that this is the second largest study to evaluate the prognostic role of different histologic patterns in eMPM and the first to directly compare prognostic impact of morphologic growth pattern nuclear grade and M/N score.

This study confirms that microcystic or tubulopapillary are associated with the longest OS.

In this study the trabecular pattern had a poor prognosis similar to solid but this is not a uniform finding in the literature.

In multivariate analysis the M/N score was a single independent prognostic factor. (But there is a significant association between solid trabecular and higher M/N scores and higher nuclear grades.) While nuclear grade 3 tumors showed a significantly shorter OS they found no significant OS difference between nuclear grade 1 and 2, supporting the new EUROCAN/IASLC proposal on a two-tier grading system.

Comment: Worth taking a look at the survival curves which emphasize the results visually. Further confirmation that there is value in grading epithelial malignant mesotheliomas (although I have never been asked for one when not given).

3. **Chang WC, Zhang YZ, Lim E, Nicholson AG. Prognostic impact of histopathologic features in pulmonary invasive mucinous adenocarcinomas. *Am J Clin Pathol.* 2020 Jul;154:88-102.**

Background: There have been very few studies which have analyzed the prognostic significance of pathologic features in invasive mucinous adenocarcinomas (IMA) or mixed IMA and non-mucinous adenocarcinomas (MMNA).

Methods: 84 IMAs and 41 MMNAs were evaluated for histologic pattern (lepidic, acinar, papillary, solid, micropapillary, cribriform), nuclear atypia, mitotic activity, presence of necrosis and LVI, amount of tumor-infiltrating inflammation and STAS.

Two tumor sizes recorded: total size and invasive size.

For NMAs with multiple foci of invasion: total size x % of non-lepidic invasive components was used to determine invasion.

Adjusted T (aT) stage using invasive size only was given for each tumor. To determine which features were to be included in the new grading system, disease-free survival (DFS) and overall survival (OS) were performed for each feature with a $P < 0.07$ considered significant. Five features were chosen (architecture, atypia, mitosis, necrosis, and LVI). A scoring scheme was devised (see table).

Table. Criteria of the Pathologic Grading System

Variable	Score			
	0	1	2	3
Differentiation		Well (Lep)	Moderate (Aci/Pap)	Poor (Sol/Mic/Cri)
Nuclear atypia		Mild	Moderate	Severe
Mitosis, /2 mm ²	<4	≥4		
Necrosis	Absent	Present		
Lymphovascular invasion	Absent	Present		

Aci: acinar; Cri: cribriform; Lep: lepidic; Mic: micropapillary; Pap: papillary; Sol: solid

Total Score	2-5	6-9
Grade	Low	High

Statistical analyses: Kaplan-Meier method was used. DFS was computed from time of surgery to recurrence or metastasis and OS calculated from time of surgery to time of death, irrespective of cause.

Results: There is a TON of data presented with numerous long detailed tables. Feel free to peruse.

Association Between Pattern and Clinicopathologic Features

- Tumors with <10% lepidic were more likely to show increased mitoses, LVI, nodal mets while >10% acinar associated with nodal mets.
- >10% micropapillary showed greater STAS and LVI.
- >10% cribriform associated with pleural and LVI and nodal mets.

Association Between Invasive Size and aT Stage with Clinicopathologic Features: When IMAs were adjusted for invasive size, 61% of T2a/b and 28.6% of T3/4 were adjusted down to T1a/b/c and 24.5% of T3/4 were adjusted to T2a/b.

Association Between Pathologic Grade and Clinicopathologic Features: High grade tumors (which turned out to be micropapillary and cribriform) significantly associated with pleural invasion, nodal mets, higher adjusted T state and TNM stage.

Survival Analyses Between IMA and MMNA:

- No significant prognostic difference observed between IMA and MMNA although pure IMAs showed worse DFS within 5 years.
- MMNAs showed that both the DFS and OS lie in between low- and high-grade IMAs.

Survival Analyses Between IMAs:

- In the IMA group, worse DFS significantly associated with T stage.
- Adjusted T stage using invasive size significantly associated with poor OS but not DFS was nonadjusted T stage with significantly associated with DFS but not OS.

Higher pathologic grade associated with poor OS but not DFS. Total size associated with poorer DFS.

Discussion: The authors showed that a two-tier grading system stratifies IMAs into two groups; > 10% micropapillary and cribriform associated with more aggressive behavior.

Suggest that remeasuring tumors so that lepidic areas viewed as noninvasive as in NMAs refines prognostic pT category stratification.

Results of MMNA analysis in this study did not show significant prognostic differences in DFS or OS between mixed and non-mixed groups although mixed tumors showed slightly better DFS at 5 years. MMNAs did develop extra pulmonary mets more often while IMAs tended to develop intrapulmonary mets. Authors summarize interesting genetic data showing that MMNAs may represent the separate tumor type.

Authors discuss limitations including use of OS rather than DFS, interobserver agreement issues.

Comment: I liked this study even though there is a tremendous amount of data. This is one of few studies digging deeper into IMAs and MMNA's. I think the bottom line makes sense, frankly, given what we have learned about non-mucinous adenocarcinomas.

4. Pagan CA, Shu CA, Crapanzano JP, Lagos GG, Stoopler MB, Rizvi NA, Heymann JJ, Sonett JR, Fernandes H, Saqi A. Synchronous Pulmonary Adenocarcinomas: correlation among morphology, next-generation sequencing/single-gene analysis molecular testing, and clinical outcomes with eighth edition AJCC criteria. *Am J Clin Pathol.* 2020 Jul;154:57-69

Background: In the most recent AJCC system, ADCA demonstrating lepidic predominant morphology including lepidic predominant adenocarcinoma, MIA or AIS are considered independent (multiple) primaries despite matching histology. CAP, IASLC and AMP do not require testing of all tumors even when seemingly similar. This study examined the degree of concordance between morphology and molecular testing among synchronous pulmonary ADCA using targeted next generation sequencing (NGS) with and without comprehensive molecular review (CMR) versus multiple single genes (non-NGS) analysis.

Methods: All consecutive NSCLCs with more than one nodule in a resection with available molecular testing (MT). MT done by standard protocol on all ADCA, using IHC, FISH, Sanger sequencing and NGS.

Concordance = (1) tumors with same histology harboring identical driver mutations or (2) tumors with different histology harboring different driver mutations or with one tumor lacking an identifiable oncogenic driver.

Discordant = (1) tumors with same histology but different drivers or one lacking identifiable driver (wild type [WT]); or (2) tumors with different histology sharing identical driver mutations.

Indeterminant=all tumors lacking identifiable mutations or when same hotspot mutations were present and CMR uninformative. All discordant cases reviewed to determine whether initial diagnosis was correct (Comprehensive histologic assessment).

- NGS used the Illumina TruSeq cancer amplicon panel. Variant analysis performed with NextGENe software with manual review by molecular genetic pathologists.
- CMR of all cases with identical hotspot mutations that underwent NGS was conducted.
- Sanger sequencing performed on specimens prior to implementation of TruSeq and in cases with insufficient DNA for NGS.

Pathologic Staging and Clinical Follow-up: the highest T, when T3 or higher, was assigned based on morphology and/or molecular results. The tumors categorized as T3, T4, or M1a when similar histology or molecular profiles were present in the same lobe, different ipsilateral lobes, or contralateral lobes, respectively. In cases with dissimilar histology, T was based on AJCC criteria (e.g., size).

> 4 mos follow-up had to be available for clinical analysis.

Results: 47 cases representing 44 patients met criteria for synchronous NSCLC resections with molecular testing in at least two tumors. All tumors were adenocarcinoma.

Similar histology=14 patients; different histology=30 patients, with multifocal adenocarcinoma with LP morphology in 3 patients.

Molecular Results

- Among 108 individual tumors sequenced using non-NGS and NGS.
- Overall, non-NGS and NGS methods without CMR were informative in 49% (23/47) of cases. With CMR, 75% (35/47) had informative comparisons in the entire cohort; among only NGS cases, 96% (22/23) were informative.
- 53% (25/47) were concordant while 21% (10/47) were discordant between morphologic and molecular classification; 26% (12/47) were indeterminant. A re-review of discordant cases led to 7 (70%) still remaining discordant.

Pathologic Stage and Follow-up

Based on MT, five patients were up-staged to T3 and five were down-staged from T3.

Discussion: *Current Guidelines:* there are no uniformly accepted guidelines for addressing the role of molecular testing in the presence of multiple synchronous tumors (AJCC recommendation notwithstanding).

Morphologic Assessment: results of the current study demonstrate 53% concordance and 21% discordance between morphologic and molecular classification; 26% (12/47) were still indeterminate, similar to prior studies. Morphologic reassessment revised results in three discordant cases.

Clinical Impact: the study demonstrates that the decision to stage by histology or molecular results may have significant clinical impact, e.g., patients with tumors of different histology but identical molecular testing results were not always referred to medical oncology and therefore did not receive potentially beneficial adjuvant chemotherapy. In discordant cases with same histology and different molecular results, patients may be unnecessarily treated with chemotherapy.

Comment: An additional study arguing for the importance of molecular testing when dealing with synchronous primary tumors.

5. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Baenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.* 2020 Jul;383:120-8.

Background: Despite wide spread interest in the pathophysiology of Covid-19 related disease, little is known about the morphologic and molecular changes of the lungs from patients who die of the disease.

Methods: Seven (7) autopsy lungs from patients who died from Covid-19 were compared to 7 autopsy lungs from patients who died of ARDS secondary to influenza A (H1N1). Lungs from patients with influenza from 2009 pandemic and were chosen for the best possible match for age, sex and disease severity. Ten lungs donated but not used for transplantation served as uninfected controls.

All lungs comprehensively analyzed with use of micro-CT, histology, multiplexed IHC, TEM and SCM, corrosion casting, and direct multiplexed gene expression analysis.

Results: All specimens from the Covid-19 group had DAD with necrosis.

- 4/7 changes were focal with only mild interstitial edema. In the other 3 the changes were severe and showed early organization.
- Influenza group showed florid DAD with massive interstitial edema and extensive fibrin deposition; 3 patients with influenza had focal organization.

Angiocentric Inflammation:

- CD3-positive T cells: similar in Covid-19 and influenza patients.
- CD4-positive cells: more frequent in patients with Covid-19 than influenza (P=0.04).
- CD8-positive cells: less numerous in Covid-19 than influenza (P=0.008).

Multiplexed analysis of inflammation-related gene expression showed some similarities and some differences between Covid-19 and influenza groups.

Alveolar capillary microthrombi 9 times as prevalent in Covid-19 versus influenza.

Intravascular thrombi in postcapillary venules seen in lower numbers of patients with Covid-19 than influenza.

Covid-19 (N=2) had involvement of all segments of vasculature as opposed to 4 lungs in influenza; in 3 Covid-19 lungs and 3 influenza combined capillary and venous thrombi were found without arterial thrombi.

Vascular findings confirmed on micro-CT of the pulmonary specimens.

Angiogenesis Observations.:

Covid-19 group: “distorted vascularity with structurally deformed capillaries with sudden changes in caliber and the presence of intussusceptive pillars.” TEM showed ultrastructural damage to the endothelium as well as intracellular SARS-CoV-2. The virus could also be identified in the extracellular space. These changes were significantly higher than in lungs from patients with influenza or controls. The density of “sprouting angiogenesis” was also higher in Covid-19 than influenza patients.

Sixty-nine (69) angiogenesis-related genes were differently regulated in Covid-19 group as compared with 26 differentially regulated in the influenza group; 45 genes had shared expression.

Discussion: There were three distinctive angiogenic features in Covid-19.

- More severe endothelial injury associated with intracellular virus and disrupted endothelial cell membranes.
- Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries.
- Significant new vessel growth through a mechanism of intussusceptive angiogenesis.
- The significance of these findings is not clear.

Comment: The CT images are worth perusing. The overall number of patients, however, is relatively small. There may be some methodologic problems as nicely highlighted in the accompanying editorial.

6. **Hariri L, Hardin CC. EDITORIAL Covid-19, angiogenesis, and ARDS endotypes. N Engl J Med. 2020 Jul;383:182-3.**

The editorial highlights the renewed interest in the pathobiology of ARDS in the setting of Covid-19 and nicely discusses the limitations of the above study.

Neoplastic

1. **Hofman V, Benzaquen J, Heeke S, Lassalle S, Poudenx M, Long E, Lantéri E, Bordone O, Lespinet V, Tanga V, Bonnetaud C, Bille Y, Ilié M, Marquette C, Barlesi F, Boutros J, Hofman P. Real-world assessment of the BRAF status in non-squamous cell lung carcinoma using VE1 immunohistochemistry: a single laboratory experience (LPCE, Nice, France). Lung Cancer. 2020;145:58-62.**

Background: International guidelines recommend BRAF mutational status be evaluated in non-squamous, NSCLC given availability of BRAF inhibitor therapy. This study is a prospective evaluation of the feasibility of systematic BRAF evaluation using IHC.

Methods: 1317 NSCLC evaluated using BRAF IHC from 2011-2019.

- BRAF status was prospectively assessed using NGS and/or pyrosequencing in 618 patients from 2012-2016. BRAFV600E and BRAF non-V600E mutated tumors detected in this cohort were retrospectively evaluated using BRAF IHC.
- 699 biopsies of NSCLC were prospectively analyzed between 2017-2019 using BRAF IHC; BRAF IHC positive tumors were then tested using a rapid BRAF specific PCR-based assay.

Results: About 3% of patients overall in this series have BRAFV600E mutations.

21/21 tumors on the first set of tumors examined (618) had 100% correlation between IHC and NGS and/or pyrosequencing. 20/24 (83%) had positive PCR for BRAF/IHC positive cases.

Discussion: BRAFV600E IHC can provide rapid sensitive results in patients being considered for BRAF inhibitor treatment.

2. **Mack PC, Banks KC, Espenschied CR, Burich RA, Zill OA, Lee CE, Riess JW, Mortimer SA, Talasaz AA, Lanman RB, Gandara DR. Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: analysis of over 8000 cases. Cancer. 2020;126:3219-28.**

Summary: Plasma based comprehensive genomic profile was performed on 8388 consecutively tested patient with advanced NSCLC. Both driver and resistance mutations were examined.

Somatic alterations detected in 86% of samples. This is similar to what was expected if the tumors were directly analyzed.

The findings support comprehensive ctDNA testing in patients incompletely tested at the time of diagnosis and as a primary option at the time of progression on targeted therapies.

3. **EDITORIAL Makarem M, Leighi NB. Molecular testing for lung adenocarcinoma: is it to adopt a “plasma-first” approach? Cancer. 2020 Jul;3176-80.**

Summary: Lengthy editorial (5 pages) discussing this article and how ctDNA fits into algorithms for first time therapy/diagnosis and recurrences.

4. **LETTER Thunnissen E, Flieder D. Morphologic logic: “filigree” and “classical” micropapillary pattern are orientation-dependent views of the same lesion. J Thorac Oncol. 2020 Jul;15(7):e120-e121.**
5. **LETTER Emoto K, Tan KS, Rekhman N, Adusumilli PS, Travis WD. The newly described filigree pattern is an expansion of the micropapillary adenocarcinoma concept rather than a proposed new subtype. J Thorac Oncol. 2020 Jul;15(7):e121-e124.**

Summary: These letters might be worth perusing. A bit of volleying back and forth on the filigree pattern of micropapillary adenocarcinoma.

6. **LETTER Thunnissen E, Marchevsky A, Rossi G, Russell PA, Blaauwgeers H, Radonic T, von der Thüsen J, Flieder D, Pelosi G. RE: Spread through air spaces (STAS) is prognostic in atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma of the lung. J Thorac Oncol. 2020 Jul;15(7):e116-e117.**
7. **LETTER Travis WD, Aly RG, Rekhtman N, Tan KS, Adusumilli PS. Spread through air spaces is prognostic in neuroendocrine lung tumors and can be distinguished from artifacts. J Thorac Oncol. 2020 Jul;15(7):e118-e120.**

Summary: Ditto. The Memorial group clarifies several misunderstandings regarding STAS. It is everything you wanted to know about STAS. The response is worth reading.

8. **Baranov E, McBride MJ, Bellizzi AM, Ligon AH, Fletcher CDM, Kadoch C, Hornick JL. A novel SS18-SSX fusion-specific antibody for the diagnosis of synovial sarcoma. Am J Surg Pathol. 2020;44:922-33.**

Summary: The authors describe the sensitivity and specificity of two novel antibodies, an SS18-SSX fusion-specific antibody (E9X9V, designed to the breakpoint) as well as an SSX-specific antibody (E5A2C, designed to the SSX C-terminus). Using IHC on whole sections from 400 tumors including 100 genetically confirmed SS cases and 300 mimics, the SS18-SSX fusion-specific antibody was positive in 95% of SS cases and in none of the controls. The SSX antibody showed strong diffuse staining in 100% of SS cases. 13 (4%) of 300 other tumors were positive, 5 of which displayed >50% nuclear staining.

In summary, a novel SS18-SSX fusion specific antibody is highly sensitive (95%) and specific (100%) for synovial sarcoma and an antibody to the SSX C-terminus is also highly sensitive (100%) but a slight less specific (96%).

IHC using the SS18-SSX antibody could replace molecular genetic testing for synovial sarcoma.

9. **Butter R, Hart NA, Hooijer GKJ, Monkhorst K, Speel EJ, Theunissen P, Thunnissen E, Von der Thüsen JH, Timens W, van de Vijver MJ. Multicentre study on the consistency of PD-L1 immunohistochemistry as predictive test for immunotherapy in non-small cell lung cancer. J Clin Pathol. 2020;73:423-30.**

Summary: The authors investigate the impact of interlaboratory and interobserver variability of IHC for the assessment of PD-L1 in NSCLC. 10 pathologists scored the tumors using tissue microarrays. The authors identify that both interlaboratory variability and interobserver variability contribute to different results. Interobserver variability showed the largest variation in the 22C3 pharmDx assay and with a 22C3 LDT. Test results when both IHC and PD-L1 scoring were performed within the same center showed more variability among centers which use the LDT than centers which use the 22C3 pharmDx assay. The most variability appeared to occur around the designated cutoffs. PD-L1 scoring is still a challenging proposition (and I am grateful I don't have to do it!).

10. **Ishihara S, Okada S, Ogi H, Kodama Y, Shimomura M, Tsenezuka H, Itoh K, Marx A, Inoue M. Programmed death-ligand 1 expression profiling in thymic epithelial cell tumors: clinicopathological features and quantitative digital image analyses. Lung Cancer. 2020;145:40-7.**

Summary: The authors correlate PD-L1 expression with thymoma subtype utilizing optical microscopy and digital image analysis. PD-L1 expression depended on the histologic subtype of TET with extensive PD-L1 expression being associated with a poor prognosis. Digital image analysis proved to be feasible. Image analysis showed better correlation in combined tumors and in thymomas but not in thymic carcinomas likely due to an under estimation in tumor regions without cytokeratin staining.

11. **Lindholm KE, Sansano-Valero I, Rodriguez JL, Ramon y Cajal S, Moran CA. Pulmonary adenofibromas: a clinicopathologic correlation of 13 cases. Am J Surg Pathol. 2020;44:917-21.**

Summary: Primary pulmonary adenofibromas are presented, from 8 women and 5 men (41-73 years, mean age 57). All had a phyllodes-like growth pattern. All tumors were negative for CD34, Bcl-2, STAT6, S-100, desmin and smooth muscle actin. In 6 cases in situ hybridization to exclude SFT was also performed and found to be negative. Authors have a fairly lengthy discussion on whether these represent the variants of SFT. Pictures are definitely worth a look if you have not seen one of these.

12. **Georgiesh T, Boye K, Bjerkehagen B. A novel risk score to predict early and late recurrence in solitary fibrous tumor. *Histopathol.* 2020;77:123-32.**

Summary: The authors indicate that one of the challenges with prior proposed scoring systems includes the fact that follow-up was relatively short in these studies, particularly in the Demicco, et al. paper. Their aim was to develop a prognostic scoring system that accounts for early and late recurrences, and they used a large cohort with long-term follow-up from a sarcoma reference center.

Table. A novel risk stratification model (G-score) for prediction of recurrence in solitary fibrous tumour

Prognostic factors	Score
Mitotic count ¹	
<4	0
≥4	2
Necrosis	
Absent	0
<50%	1
≥50%	2
Gender	
Female	0
Male	1
Risk score	Total score
Low	0
Intermediate	1-2
High	3-5

¹Mitotic figures per 10 high-power fields of the microscope

The authors found that mitotic count, necrosis and gender were independent prognostic markers of recurrence and suggest that their system should be validated in other cohorts with sufficient follow-up time.

13. **Miyana A, Masuda M, Motoi N, Tsuta K, Nakamura Y, Nishijima N, Watanabe SI, Asamura H, Tsuchida A, Seike M, Gemma A, Yamada T. Whole-exome and RNA sequencing of pulmonary carcinoid reveals chromosomal rearrangements associated with recurrence. *Lung Cancer.* 2020;145:85-94.**

Summary: The authors demonstrate 8 fusion genes in primary pulmonary carcinoid tumors associated with metastases; and 14 genes upregulated in 5 carcinoids that relapsed after surgical excision.

It will be essential to validate the clinical significance of these genetic changes in a larger cohort.

Non-Neoplastic

1. **Barth RF, Xu X, Muja LM. A call to action: the need for autopsies to determine the full extent of organ involvement associated with COVID-19. *Chest.* 2020:43-44.**

Summary: Editorial calling for more autopsies to be done on COVID-19 patients.

2. **Bösmüller H, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, Frauenfeld L, Vogelsberg A, Klingel K, Fend F. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. *Virchows Arch.* 2020 Jun30:1-9.**

Summary: Authors report 4 fatal cases of COVID-19. The early disease was characterized by neutrophils, capillaritis, and microthrombosis. Later stages appeared to show DAD with ongoing intravascular thrombosis, occasional areas of infarction and

other laboratory features of DIC. In late stages OP with extensive metaplasia was identified. Viral RNA was identified in the lung and endothelial cells and pneumocytes.

3. **Verleden SE, Vanstapel A, De Sadeleer L, Weynand B, Boone M, Verbeken E, Piloni D, Van Raemdonck D, Ackermann M, Jonigk DD, Verschakelen J, Wuyts WA. Quantitative analysis of airway obstruction in lymphangioleiomyomatosis. Eur Respir J. 2020;56:1901965.**

Summary: ex vivo CT is done on lungs frozen in fumes of liquid nitrogen while microCT is done on air inflated and subsequently air dried specimens. The authors use ex vivo CT, microCT and histology to look at the site, extent and nature of airway obstruction in LAM explants compared with match controls. Ex vivo CT demonstrated a reduced number of airways. Whole-lung microCT confirmed the presence of a three- to four-fold reduction in the number of airways. Specimen microCT analysis further demonstrated a four-fold decrease in the number of terminal bronchioles. Serial microCT and histology images directly showed loss of functional airways by collapse of airways on the cysts and filling of the airway by exudate. They conclude that LAM lungs show a three- to four-fold decrease in the number of small airways caused by cystic destruction which contributes to the progressive loss of pulmonary function;

The images are worth reviewing. The authors are probably on to something.

4. **EDITORIAL Bourdin A, Gamez AS, Vachier I, Crestani B. LAM is another small airway disease: lessons from microCT. Eur Respir J. 2020;56:2002612.**

Summary: The editorial speculates on the significance of this finding and how it might be clinically relevant.

After reading this paper I kind of wish I would have selected it as one of the main papers as I think there is a lot here worth considering.

Reviews and Case Reports

1. **Weinberger JF, Lo YC, Vargas SO, Cagnina RE. An unusual cause of mosaic attenuation. Am J Respir Crit Care Med. 2020 Jul;202(1):128-9.**

Leukemia (AMML) causing mosaicism in a 68 year old woman. Nice images.

2. **Zhao J, Bhatnagar V, Ding L, Atay SM, David EA, McFadden PM, Stamnes S, Lechholz-Zey E, Wightman SC, Detterbeck FC, Kim AW. A systematic review of paraneoplastic syndromes associated with thymoma: treatment modalities, recurrence, and outcomes in resected cases. J Thorac Cardiovasc Surg. 2020 Jul;160(1):306-14.**

A good reference paper for paraneoplastic syndromes, that might be useful to have for lectures and education. Table 1 is a nice summary.

3. **Smith AP, Dueber JC, Allison DB. A diagnostic review of carcinomas and sarcomas of the mediastinum: making the diagnosis on fine-needle aspiration and core needle biopsy specimens. Semin Diagn Pathol. 2020;37:187-98.**
4. **VandenBussche CJ. A review of mediastinal lesions encountered on fine needle aspiration and small biopsy specimens. Semin Diagn Pathol. 2020;37:155.**
5. **Reynolds JP, Liu S. Fine needle aspiration of mediastinal germ cell tumors. Semin Diagn Pathol. 2020;37:174-8.**
6. **Zhang ML, Shoani AR. Lymphomas of the mediastinum and their differential diagnosis. Semin Diagn Pathol. 2020;37:156-65.**
7. **Stewart BD, VandenBussche CJ, Leon ME. Benign lesions of the mediastinum: a review with emphasis on cytology and small biopsy specimens. Semin Diagn Pathol. 2020;37:199-210.**
8. **Illei PB, Shyu S. Fine needle aspiration of thymic epithelial neoplasms and non-neoplastic lesions. Semin Diagn Pathol. 2020;37:166-73.**

Articles 3-8 form a set focusing on cytologic evaluation of mediastinal lesions. Might be good reading for trainees and a great reference for others.

9. Gaeta JM, De Las Nueces D, Munson DG, Barocas JA, Walsh KE. Case 21-2020: A 66-year-old homeless man with Covid-19. *N Engl J Med.* 2020;383:170-8.

I was struck by the free standing tent units used to house some COVID patients in Boston!

10. Shao C, Liu H, Meng L, Sun L, Wang Y, Yue Z, Kong H, Li H, Weng H, Lv F, Jin R. Evolution of severe acute respiratory syndrome coronavirus 2 RNA test results in a patient with fatal coronavirus disease 2019: a case report. *Human Pathol.* 2020;101:82-8.

Another COVID paper to add to your list!

11. Stone JR, Tran KM, Conklin J, Mino-Kenudson M. Case 23-2020: A 76-year-old woman who died from Covid-19. *N Engl J Med.* 2020;383:380-7.

And another....this one focuses on CV affects.

12. Newton-Cheh C, Zlotoff DA, Hung J, Rupasov A, Crowley JC, Funamoto M. Case 24-2020: A 44-year-old woman with chest pain, dyspnea, and shock. *N Engl J Med.* 2020;383:475-84.

And another....this one focuses on CV affects even more.

13. Sarwate M, Vrbenska A, Cummings K, Tazelaar HD. Unusual pneumoconiosis in two patients with heavy print toner, and paper dust exposure. *Am J Ind Med.* 2020;1-7.

Take a look at the 4 color toner in the lungs one patient and GIP related to toner in another. ☺ You won't be disappointed.

14. Alzghoul BN, Innabi A, Mukhtar F, Jantz MA. Rapid resolution of severe vaping-induced acute lipoid pneumonia after corticosteroid treatment. *Am Respir Crit Care Med.* 2020;202(2):e32-e33.

ARRRGHHH.

15. Satou A, Notohara K, Zen Y, Nakamura S, Yoshino T, Okazaki K, Sato Y. Clinicopathological differential diagnosis of IgG4-related disease: a historical overview and a proposal of the criteria for excluding mimickers of IgG4-related disease. *Pathol Int.* 2020;70(7):391-402.

The authors do a nice job of separating out the various patterns including

- Plasma cell/Castleman disease type
- Reactive follicular lymphoid hyperplasia type
- Interfollicular expansion and immunoblastosis type
- Progressive transformed germinal center type
- Inflammatory pseudotumor type

They also suggest excluding criteria (see table below).

Table. Exclusion criteria for IgG4-related disease

Cases that are present with any one of the clinical or pathological findings listed below cannot be categorized as definite IgG4-RD, although they may meet the diagnostic criteria for IgG4-RD
<p>Clinical findings</p> <ul style="list-style-type: none"> • Continuing elevated serum level of CRP (≥ 1.0 mg/dL)[†] • Elevated serum level of IgA[‡] • Elevated serum level of IgM[‡]
<p>Pathological findings</p> <ul style="list-style-type: none"> • Sheet-like proliferation pattern of mature plasma cells • High degree of hemosiderin deposition • Neutrophilic infiltration

[†]Continuing elevation of uncertain cause.

[‡]Serum level above normal range is defined as 'elevated'. Reference value of each institution should be applied.