Journal Club

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Articles for Discussion

Mengoli MC, et al (last author: Thomas V. Colby). Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) syndrome and carcinoid tumors with/without NECH: A clinicopathologic, radiologic, and immunomolecular comparison study. Am J Surg Pathol 2018;42:646–655

Background:
- o DIPNECH
    - o Aguayo (1992)
        - ▪ Six patients
            - • Diffuse hyperplasia of pulmonary NE cells, multiple carcinoid tumorlets, and peribronchiolar fibrosis obliterating small airways
            - • Cough, exertional dyspnea, diffuse reticulonodular infiltrates, airflow obstruction
            - • Absence of other concomitant lung diseases
    - o WHO (2015)
        - ▪ Generalized proliferation of pulmonary NE cells
            - • May be confined to the mucosa of airways or
            - • May form tumorlets and carcinoids
    - o Marchevsky et al (2015)
        - ▪ Multifocal NECH (at least 5 NE cells in at least 3 bronchioles) and
        - ▪ 3 or more carcinoid tumorlets
    - o Rossi et al (2016)
        - ▪ Syndrome of unknown cause manifesting with distinct clinical, functional, radiologic, and pathologic features

Objective:
- o To compare clinical, radiologic, histologic, immunohistochemical, and molecular features of DIPNECH and isolated carcinoids with/without NECH

Methods:
- o 151 cases (77 females and 74 males)
    - o 19 with DIPNECH and
    - o 132 with carcinoids with/without NECH

Results:
- o Patients with DIPNECH were more likely
    - o To be females, nonsmokers, and symptomatic
    - o To have an obstructive/mixed respiratory defect, peripheral location of the lesions, air trapping on chest computed tomography, and constrictive bronchiolitis on histology

Conclusion:
- o The authors conclude that DIPNECH with airway disease differs significantly from sporadic carcinoids with or without NECH in terms of demographic, clinical, radiologic, and immunopathologic features
- o They suggest "the term DIPNECH be limited to cases presenting with respiratory symptoms, functional and/or radiologic abnormalities, and constrictive bronchiolitis on histology"

My take-home message:
- o This is a classic example of circular argument; patients with DIPNECH were more likely to be symptomatic in this study, because clinical symptoms were one of the selection criteria
- o Nevertheless, it is reasonable to go back to Aguayo's original description and define DIPNECH as a clinicopathological syndrome

Amatya VJ, et al. Glypican-1 immunohistochemistry is a novel marker to differentiate epithelioid mesothelioma from lung adenocarcinoma. Mod Pathol 2018;31:809–815

Objective:
- o To investigate glypican-1 expression by immunohistochemistry using a commercially available antibody

Materials:
- o 82 cases of epithelioid mesothelioma
- o 97 cases of lung adenocarcinoma

Methods:
- o Polyclonal glypican-1 antibody (Proteintech)

Results:
- o All 82 cases of epithelioid mesothelioma showed glypican-1 expression, most with diffuse and strong reactivity
- o Three of 97 cases of lung adenocarcinoma showed focal glypican-1 expression
- o Sensitivity and specificity:

Mesothelioma marker	Sensitivity (%)	Specificity (%)
Glypican-1	100	97
Calretinin	99	81
D2-40	97	93
WT1	86	100

My take-home message:
- o This is a polyclonal antibody, which has disadvantages
- o However, it is probably worth a try

Churg A, et al (last author: Sanja Dacic). Malignant mesothelioma in situ. Histopathology 2018:72,1033–1038

Background:
- o The existence of malignant mesothelioma in situ (MIS) is often postulated, but there are no accepted morphological criteria for making such a diagnosis

Objective:
- o To report two cases that appear to be true MIS on the basis of in-situ genomic analysis

Results:
- o Case 1 (70-year-old woman)
  - o Repeated unexplained pleural unilateral effusions
  - o Two thoracoscopies 9 months apart revealed only visually normal pleura
  - o Biopsies from both thoracoscopies showed only a single layer of mildly reactive mesothelial cells
  - o Loss of BRCA1-associated protein 1 (BAP1)
  - o Loss of cyclin-dependent kinase inhibitor 2 (CDKN2A) (p16) by FISH
  - o NF2 was not deleted by FISH
  - o 28% of the mesothelial cells showed hyperploidy
  - o Six months after the second biopsy the patient has persisting effusions but no evidence of pleural malignancy on imaging
- o Case 2 (60-year-old woman with a past history of breast cancer)
  - o Ascites and minimal omental thickening on imaging
  - o No visual evidence of tumor at laparoscopy
  - o Omental biopsy showed a single layer of minimally atypical mesothelial cells with rare tiny foci of superficial invasion of fat
  - o Loss of nuclear BAP1 in all surface mesothelial cells and invasive cells by IHC
  - o Loss of CDKN2A by FISH
  - o NF2 was not deleted by FISH.

Conclusions:
- o These cases show that morphologically bland single-layered surface mesothelial proliferations with molecular alterations seen previously only in invasive malignant mesotheliomas exist, and presumably represent malignant MIS
- o More cases are needed to understand the frequency of such changes and the time course over which invasive tumor develops

My take-home message:
- o These are well documented cases, which appear to represent legitimate MIS

Noll B, et al. Programmed death ligand 1 testing in non–small cell lung carcinoma cytology cell block and aspirate smear preparations. Cancer Cytopathol 2018;126:342-52

Background:
- o Immune checkpoint inhibitors targeting the programmed cell death 1 (PD-1) receptor and its ligand, programmed death ligand 1 (PD-L1), have emerged as a therapeutic approach for patients with non–small cell lung carcinoma (NSCLC).
- o PD-L1 expression, assessed by immunohistochemistry (IHC), is used to select patients for PD-1/PD-L1 inhibitor therapy.
- o Most studies have been performed with histology specimens, with limited data available on the performance in cytology specimens.

Objective:
- o To evaluate PD-L1 in cytology specimens
- o To compare the results with those from paired core-needle biopsy for concordance

Materials and Methods:
- o Forty-one NSCLC fine-needle aspiration cases that had paired core needle biopsy specimens with PD-L1 IHC were selected
- o A Papanicolaou-stained direct smear and a cell block section from each case were stained with a Dako PD-L1 pharmDx antibody (clone 22C3)
- o Only slides with 100 or more tumor cells (37 smears and 38 cell blocks) were evaluated
- o Tumor proportion scores (TPS) were assessed on the basis of the partial/complete membranous staining of tumor cells and were correlated with those of paired core-needle biopsy

Results:
- o Smears (37)
  - o PD-L1 negative smears (9)
    - ▪ 9 (100%) were concordant with the paired core needle biopsy
  - o Smears with PD-L1 expression (28)
    - ▪ 27 showed a TPS similar to that of the paired core needle biopsy
    - ▪ 1 showed a discordant TPS
- o Cell blocks (38)
  - o PD-L1 negative cell blocks (9)
    - ▪ 9 (100%) were concordant with the paired core-needle biopsy
  - o Cell blocks with PD-L1 expression (29)
    - ▪ 22 showed a TPS similar to that of the paired core needle biopsy
    - ▪ 6 showed a discordant TPS
    - ▪ 1 core needle biopsy was negative

Conclusions:
- o The results show that NSCLC cytology samples evaluated for PD-L1 have high concordance with paired core-needle biopsy samples and can be used for assessing PD-L1 expression

My take-home message:
- o Both cell blocks (we use) and smears (we do not use) can be used for PD-L1 staining

von der Thüsen JH, et al. The histomorphological spectrum of restrictive chronic lung allograft dysfunction and implications for prognosis. Mod Pathol 2018;31:780–790

Background:
- o Chronic lung allograft dysfunction continues to be the main contributor to poor long-term allograft survival after lung transplantation
- o The restrictive phenotype of chronic lung allograft dysfunction carries a particularly poor prognosis
- o Little is known about the pathogenetic mechanisms involved in restrictive chronic lung allograft dysfunction

Objective:
- o To perform histomorphological and immunohistochemical analysis of restrictive chronic lung allograft dysfunction lungs

Materials and Methods:
- o Explant lung tissue from 21 restrictive chronic lung allograft dysfunction patients was collected and histopathologic patterns of rejection, fibrosis and vascular changes were scored after routine histochemical stains and additional immunohistochemistry for endothelial markers and C4d

Results:
- o Histologic findings
  - o Acute cellular rejection: 75%
  - o Obliterative bronchiolitis: 55%
  - o Pleuroparenchymal fibro-elastosis: 10
  - o Nonspecific interstitial pneumonia: 5
  - o Fibrosis induced subpleural/paraseptal emphysema: 5
  - o Other
    - ▪ Fibrinous alveolar exudates were frequently seen in association with fibrosis (n=6), but no diffuse alveolar damage was found
    - ▪ Evidence of microvascular damage was present in most cases
- o Survival
  - o An emphysematous pattern of fibrosis was associated with a better survival (P=0.0030),
  - o Fibrinous exudates were associated with a worse survival (P=0.0007).

Conclusion:
- o "In addition to the previously described nonspecific interstitial pneumonia and pleuroparenchymal fibro-elastosis patterns in restrictive chronic lung allograft dysfunction, we are the first to describe a pattern of fibrosis-induced subpleural/paraseptal emphysema"
- o This pattern confers a better survival, whereas fibrinous exudates are associated with a worse survival

Neoplastic

Lin G, et al. Acinar-predominant pattern correlates with poorer prognosis in invasive mucinous adenocarcinoma of the lung. Am J Clin Pathol 2018;149:373-378

Objective:
- To investigate prognostic and clinicopathologic aspects of invasive mucinous adenocarcinoma (IMA) with different growth patterns (lepidic, acinar and papillary)

Materials and Methods:
- Of 2,236 patients with primary lung adenocarcinoma
  - 16 lepidic predominant IMAs
  - 10 acinar predominant IMAs
- Data regarding clinicopathologic characteristics, computed tomography (CT) features, and prognosis were collected.

Results:
- No statistically significant difference was noted in sex, age, smoking history, and T classification between the two groups
- The proportion of lymph node metastasis was significantly higher in acinar-predominant IMA
- CT
  - Similar
  - Air bronchogram was relatively specific for lepidic predominant IMA
- Survival analysis showed that acinar predominantnIMA had a poorer prognosis

Conclusions:
- Lepidic predominant and acinar predominant are two different subtypes of IMA
- Acinar predominant IMA is associated with lymph node metastasis and a poorer prognosis

My take-home message:
- I am still not convinced that it is worth splitting IMAs
- I am surprised that there were no IMAs with predominantly micropapillary growth pattern

Rosenbaum JN, et al. Genomic heterogeneity of ALK fusion breakpoints in non-small-cell lung cancer. Mod Pathol 2018;31:791–808

Background:
- In lung adenocarcinoma, EML4-ALK inversion results in a fusion protein with a constitutively active ALK kinase domain
- Evidence of ALK rearrangement occurs in a minority (2–7%) of lung adenocarcinoma, and only ~ 60% of these patients will respond to targeted ALK inhibition by drugs such as crizotinib and ceritinib
- Clinically, targeted anti-ALK therapy is often initiated based on ALK rearrangement detected by FISH
- "At the genomic level, however, ALK rearrangements are heterogeneous, with multiple potential breakpoints in EML4, and alternate fusion partners"

Objective:
- To characterize genomic breakpoints

Materials and Methods:
- 33 FISH-positive lung adenocarcinomas

- Next-generation sequencing of DNA and RNA
- ALK immunohistochemistry

Results:
- Of these 33 cases, 29 (88%) had detectable DNA level ALK rearrangements involving EML4, KIF5B, or non-canonical partners including ASXL2, ATP6V1B1, PRKAR1A, and SPDYA
- Survival analysis of patients treated with targeted ALK inhibitors demonstrates a significant difference in mean survival between patients with and without next-generation sequencing confirmed EML4-ALK rearrangements (20.6 months vs 5.4 months, Po0.01).

Conclusion:
- The data demonstrate abundant genomic heterogeneity among ALK-rearranged lung adenocarcinoma which may account for differences in treatment response with targeted ALK inhibitors

Tabbo F, et al. Cell of origin markers identify different prognostic subgroups of lung adenocarcinoma. Hum Pathol 2018;75:167–178

Objective:
- To evaluate whether a panel of 6 antibodies (TTF1, SP-A, napsin A, MUC5AC, CDX2 and CK5), which define the putative "cell of origin," identifies prognostic subgroups among lung adenocarcinoma (ADC) patients
- To assess how these markers correlate with common genetic mutations, classical histology and clinicopathological characteristics

Materials and Methods:
- A large cohort of ADC specimens were screened
- The authors evaluated
    - Marker positivity by immunohistochemistry
    - Morphological appearance by light microscopy
    - Presence of "hotspot" mutations of candidate genes by Sequenom technology
- Antibodies of alveolar differentiation
    - TTF-1, napsin A, SP-A
- Antibodies of bronchiolar differentiation
    - MUC5AC, CDX-2, CK5
- Uni- and multivariable-adjusted comparisons were performed to evaluate possible predictors of survival

Results:
- Four subgroups were identified
    - Alveolar
    - Bronchiolar,
    - Mixed
    - Null type
- Alveolar differentiation was more common in young female patients

Conclusion:
- According to the authors, ADC subtypes based on this 6-antibody panel efficiently predict survival

Nicholson AG, et al. Eighth edition staging of thoracic malignancies: Implications for the reporting pathologist. Arch Pathol Lab Med 2018;142:645–661

Background:
- o The Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer, in conjunction with the International Mesothelioma Interest Group, the International Thymic Malignancy Interest Group, and the Worldwide Esophageal Cancer Collaboration, developed proposals for the 8th edition of their respective tumor, node, metastasis (TNM) staging classification systems
- o These proposals have mostly been accepted by the Union for International Cancer Control and the American Joint Committee on Cancer and incorporated into their respective staging manuals (2017)
- o The Union for International Cancer Control recommended implementation beginning in January 2017
- o However, the American Joint Committee on Cancer has deferred deployment of the eighth TNM until January 1, 2018, to ensure appropriate infrastructure for data collection

Objective:
- o To review these changes and discuss issues for the reporting pathologist

Conclusions:
- o Pathologists should become familiar with and start to incorporate the 8th edition staging in their daily reporting of thoracic cancers

Flockerzi FA, et al. FGFR1 gene amplification in squamous cell carcinomas of the lung: a potential favorable prognostic marker for women and for patients with advanced cancer. Virchows Archiv 2018;472:759–769

Background:
- o In squamous cell carcinoma (SCC) of the lung, mutations within the genes of fibroblast growth factor receptors (FGFR) such as K660N/K660E in FGFR2 and R248C/S249C in FGFR3 and FGFR1 gene amplification have been described, but their prognostic relevance still remains unclear

Objective:
- o To detect the mutation frequencies and to define their prognostic value for associated clinicopathologic features and survival of patients

Materials and Methods:
- o Resected ΔNp63/p40-positive SCC of the lung (n = 101) were screened
  - o For FGFR1 gene amplification by fluorescence in situ hybridization performed on formalin-fixed paraffin embedded tissues and
  - o For the presumed driver mutations in genes of FGFR2 and FGFR3 by PCR and Sanger sequencing

Results:
- o Twenty-two of 101 SCCs (22%) were positive for amplification based on a FGFR1/centromere (chromosome 8) ratio > 2.0 or higher
- o In advanced tumor stages (III–IV), the overall survival of patients carrying FGFR1 gene amplification was significantly higher
- o Among women, FGFR1 gene amplification was significantly associated with longer overall survival

- The presence of FGFR1 gene amplification was associated with patient age (65 versus 69 years, p = 0.046), but not with gender, tumor stage, histologic subtype, tumor grade, or ΔNp63/p40 immunoreactivity
- The S249C mutation in the FGFR3 gene was identified in one out of 101 SCCs (1%); the K600N, K660E, or R248C mutations were not identified

Conclusions:
- These results suggest that FGFR1 gene amplification is a frequent alteration in SCC of the lung and appears to be a favorable prognostic marker for women and particularly for patients with advanced SCC of the lung (stage III–IV)

Dustin E et al. Regional lymph node sampling in lung carcinoma: a single institutional and national database comparison. Hum Pathol 2018;75:55–62

Background:
- Assessing regional lymph node metastasis is a key component of lung carcinoma staging and prognostication
- Recent guidelines have suggested a quality metric of 10 total regional lymph nodes sampled with each stage I-II primary lung carcinoma resection
- However, the extent of mediastinal lymph node sampling remains controversial

Objective:
- To assess factors contributing to regional lymph node counts and effect on overall patient survival

Materials and Methods:
- An institutional cohort of 888 cases and the Surveillance, Epidemiology, and End Results national cancer registry (10 856 cases)

Results:
- The distribution of total lymph node counts in lobectomy and pneumonectomy cases was variable with a median of 10 and an interquartile range of 7 to 14
- Multiple clinical and pathologic factors correlated with total regional node counts
- Total lymph node counts of at least 10 in the institutional cohort did not correlate with significant differences in overall survival as compared with node counts of less than 10
- In the Surveillance, Epidemiology, and End Results database, although 0 regional lymph nodes were correlated with reduced overall survival, no significant difference was detected for 1 to 9 versus at least 10 nodes

Conclusion:
- Lymph node counts for primary lung carcinoma are driven by surgical, pathologic, and biologic variability
- No evidence for a meaningful quality metric of 10 total regional lymph nodes at the institutional and national registry levels

Ali RH, et al. Metastatic non-small cell lung carcinoma a mimic of primary breast carcinoma—case series and literature review. Virchows Arch 2018;472:771–777

Background:
- Metastatic tumors may be difficult to distinguish from primary breast carcinoma (PBC)

Objective:
- To study metastases to the breast of pulmonary origin

Methods and Results:
- o Sixteen metastatic lung tumors to the breast were identified including12 non-small cell lung carcinomas (NSCLC), one large cell neuroendocrine carcinoma, one atypical carcinoid, and two small-cell carcinomas
- o Adenocarcinoma was the most frequent among the NSCLCs (11/14)

Conclusions:
- o Even in the absence of a clinical history of lung cancer, metastatic pulmonary adenocarcinoma to the breast should be considered in at least one of the following scenarios
  - o Single or multiple well circumscribed lesions of the breast that lack an in situ component and that are accompanied by distant metastases but negative axillary lymph nodes
  - o Breast tumors that are triple negative yet not high-grade
  - o Breast tumors presenting as stage 4 disease and/or having an unusually aggressive clinical course on standard breast therapy

Gagné A, et al. Comprehensive assessment of PD-L1 staining heterogeneity in pulmonary adenocarcinomas using tissue microarrays: Impact of the architecture pattern and the number of cores. Am J Surg Pathol 2018;42:687–694

Background:
- o Checkpoint inhibitors directed against programmed death receptor 1 (PD-1) and its ligand (PD-L1) changed the treatment of advanced lung non–small cell carcinomas
- o The decision to treat patients is influenced by PD-L1 expression by tumor cells, but evidence indicates that this staining is heterogenous within a tumor
- o As PD-L1 staining is tested mostly on biopsies, false negative results can occur due to sampling issues

Objective:
- o To establish the clinical impact of this heterogeneity

Materials and Methods:
- o 241 patients who underwent pulmonary resection for adenocarcinoma were selected
- o Tissue microarrays were constructed with five 1 mm cores representative of the histologic patterns observed in each tumor and stained for PD-L1
- o For each core, the histologic pattern and the percentage of PD-L1 positive tumor cells were noted
- o Staining heterogeneity was defined as cases with both positive and negative cores at positivity thresholds of 1%, 10%, and 50% of tumor cells

Results:
- o At the 50% cut-off, 37.8% of patients were PD-L1 positive
- o Among patients with 1 negative core, 26.5% also had a positive core and could have been misclassified based on 1 biopsy
- o Mean staining of PD-L1 was higher in solid (47.9%) and micropapillary (24.2%) patterns and was lower in acinar (14.1%), papillary (3.4%), and lepidic (6.4%) architectures

Conclusions:
- o A significant proportion of patients presented a heterogenous staining for PD-L1
- o Obtaining additional cores from a tumor could help to better assess the PD-L1 status

Ng Kee Kwong F, et al. Expression of PD-L1 correlates with pleomorphic morphology and histological patterns of non-small-cell lung carcinomas. Histopathology 2018:72, 1024–1032

Objective:
- To prospectively collect data on the immunohistochemical profile of tumors assessed in our institution and to correlate this with morphological tumor features

Methods and Results:
- Immunohistochemistry for programmed death-ligand 1 (PD-L1) was considered to be adequate when >100 tumor cells were seen microscopically
- When adequate, PD-L1 staining was scored as <1%, ≥1–49% or ≥50% positive membrane staining within tumor cells only
- There were 197 assessable cases, of which 87% of those with pleomorphic features (n = 39) showed ≥50% positivity for PD-L1 expression, as compared with only 33% of cases without pleomorphic features (90% versus 25% in resected cases)
- Further correlation of PD-L1 expression with architectural patterns within the tumors was performed in 74 adenocarcinoma resections
- All invasive mucinous adenocarcinomas scored <1%
- All lepidic components in non-mucinous adenocarcinoma resections scored <1%
- Thirty-five per cent of the acinar/papillary components and 53% of the solid/micropapillary components were positive for PD-L1 expression.

Conclusions:
- There are significant differences in PDL1 expression in relation to histological patterns, with particularly high levels in those with pleomorphic features and low/undetectable levels in invasive mucinous adenocarcinomas and the lepidic components of non-mucinous adenocarcinomas
- Assessment of PDL1 expression in a resected adenocarcinoma with a lepidic component may therefore not be reliable when immumodulatory therapy for recurrent disease is being considered, and either re-biopsy or limiting assessment to the invasive component may be more appropriate

Rami-Porta R, et al. Lung cancer staging: a concise update. Eur Respir J 2018;51:1800190

Review article

Nonneoplastic Lung

Swarr DT, et al. Novel molecular and phenotypic insights into congenital lung malformations. Am J Respir Crit Care Med 2018;197:1328–1339

Objectives:
- To provide insight into the molecular pathogenesis of congenital lung malformations through analysis of cell-type and gene expression changes in these lesions

Methods:
- Clinical data, and lung tissue for DNA, RNA, and histology, were obtained from 58 infants undergoing surgical resection of a congenital lung lesion
- Transcriptome-wide gene expression analysis was performed on paired affected and unaffected samples from a subset of infants (n = 14)
- A three-dimensional organoid culture model was used to assess isolated congenital lung malformation epithelium (n = 3).

Results:
- Congenital lung lesions express higher levels of airway epithelial related genes, and dysregulated expression of genes related to the Ras and PI3K–AKT–mTOR (phosphatidylinositol 3-kinase–AKT–mammalian target of rapamycin) signaling pathways
- Immunofluorescence confirmed differentiated airway epithelial cell types throughout all major subtypes of congenital lung lesions, and three-dimensional cell culture demonstrated a cell-autonomous defect in the epithelium of these lesions

Conclusions:
- This study provides the first comprehensive analysis of the congenital lung malformation transcriptome and suggests that disruptions in Ras or PI3K–AKT–mTOR signaling may contribute to the pathology through an epithelial cell-autonomous defect

Paola da Costa Souza, et al (last author: Capelozzi VL). Comprehensive analysis of immune, extracellular matrices and pathogens profile in lung granulomatosis of unexplained etiology. Hum Pathol 2018;75:104–115

Objective:
- To analyze the type 1 and type 2 T helper (Th1/Th2) cytokines (including interleukins), immune cellular, matrix profile, and pathogens in granulomas with unexplained etiology compared to those with infectious and noninfectious etiology

Materials and Methods:
- Surgical lung biopsies from 108 patients were retrospectively reviewed
- Histochemistry, immunohistochemistry, immunofluorescence, morphometry and polymerase chain reaction were used, respectively, to evaluate total collagen and elastin fibers, collagen I and III, immune cells, cytokines, matrix metalloproteinase–9, myofibroblasts, and multiple usual and unusual pathogens

Results:
- No relevant polymerase chain reaction expression was found in unexplained granulomas
- A significant difference was found between the absolute number of eosinophils, macrophages, and lymphocytes within granulomas compared to uninvolved lung tissue

- Granulomas with unexplained etiology (UEG) presented increased number of eosinophils and high expression of interleukins (ILs) IL-4/IL-5 and transforming growth factor–β
- In sarcoidosis, CD4/CD8 cell number was significantly higher within and outside granulomas, respectively; the opposite was detected in hypersensitivity pneumonitis
- Again, a significant difference was found between the high number of myofibroblasts and matrix metalloproteinase–9 in UEG, hypersensitivity pneumonitis, and sarcoidosis compared to granulomas of tuberculosis
- Granulomas of paracoccidioisis exhibited increased type I collagen and elastic fibers

Conclusion:
- Th1 immune cellular profile was similar among granulomas with unexplained, infectious, and noninfectious

My take-home messge:
- This study seems to confirm that it is not worth doing PCR in granulomas of undetermined etiology

Mäkelä K, et al. Analysis of the histologic features associated with interobserver variation in idiopathic pulmonary fibrosis. Am J Surg Pathol 2018;42:672–678

Background:
- "The histologic manifestation of idiopathic pulmonary fibrosis (IPF) is usual interstitial pneumonia (UIP), which is a good prognostic determinant of survival"
- "According to the current international guidelines, the histologic features of suspected IPF/UIP are divided into 4 categories: UIP, probable UIP, possible UIP, and not UIP pattern"

Materials and Methods:
- Four pulmonary pathologists who were blinded to clinicoradiologic information reevaluated 50 surgical lung biopsies, 6 explanted lung, and 4 autopsy samples
- Additional histologic features atypical for UIP were also evaluated and compared with clinicoradiologic information
- The interobserver agreement of pathologists was examined by Cohen kappa (κ) coefficient
- The survival of the patients was estimated with Kaplan-Meier curves.

Results:
- The histologic reevaluation indicated that 38 of 60 patients (63.3%) had definite UIP
- Inflammation was the most common additional histologic finding (15/60, 25.0%)
- The interobserver agreement on histologic diagnosis ranged from slight (κ=0.044) to substantial (κ=0.779).
- The interobserver agreement varied extensively with regard to the presence of giant cells
- The observed histologic features displayed no association with radiologic patterns or survival
- Definite UIP and honeycombing findings in high-resolution computed tomography correlated with poor prognosis

Conclusion:
- A high level of interobserver variability was observed between pathologists, even in this well defined cohort of IPF patients, which highlights the importance of multidisciplinary decision making in IPF diagnostics and stresses the need for a reassessment of the histologic criteria

My take-home message:
- I am surprised that this study has been published in its current form.
- This very first sentence of the abstract seems to be incorrect; why do the authors say that UIP is "a good prognostic determinant of survival"?

- Also, UIP, probable UIP, possible UIP, and not UIP pattern were used in the study by Raghu et al, but most pulmonary pathologists I know do not use these categories in the everyday practice

Kato T, et al. A 56-year-old woman with multiple pulmonary cysts and severe chest pain. Chest 2018;153:e105-e112

Case report of pulmonary light chain deposition disease associated with multiple myeloma
Hochhegger B, et al. Thoracolithiasis: A rare cause of multiple nodules. Am J Respir Crit Care Med 2018;197:1212–1213

Case report.

Pleura

Otsuki T, et al. Aminopeptidase N/CD13 as a potential therapeutic target in malignant pleural mesothelioma. Eur Respir J 2018; 51:1701610

Background:
- Aminopeptidase N (APN)/CD13 promotes tumour angiogenesis and is associated with poor prognosis; however, its clinical significance in malignant pleural mesothelioma
- (MPM) remains unclear

Objective:
- To evaluate the association between immunohistochemical APN/CD13 expression and survival in MPM

Materials:
- 37 consecutive patients with surgically resected MPM

Results:
- High tumour APN/CD13 expression was associated with poor prognosis in MPM patients

Conclusion:
- The results implicate APN/CD13 is in the aggressive behavior of MPM

Rrapaj E, et al. Expression analysis of HMGB1 in histological samples of malignant pleural mesothelioma. Histopathology 2018;72;1039–1050

Aims:
- High mobility group box 1 (HMGB1) is a chromatin structural protein, expressed ubiquitously in the nuclei of mammalian cells
- When transported extracellularly, it acts as a tumor suppressor and oncogenic protein
- In malignant pleural mesothelioma (MPM), high serum levels of HMGB1 have been related to a poor prognosis

Objective:
- To evaluate the significance of HMGB1 expression in MPM tissues

Methods and results:
- Biopsy samples from 170 patients with MPM were assessed by immunohistochemistry and reverse transcription–polymerase chain reaction (RT–PCR) to evaluate HMGB1 protein and gene expression
- The expression level of HMGB1 protein was scored using a semiquantitative system that sums the intensity (0–3) and the percentage (from 0 to 4) of positively stained cells in nuclei, cytoplasm and in both
- The final score was considered as high (>3) or low (<3) expression
- Gene expression levels were calculated using the DDCt method
- High expression levels of HMGB1 as total ($P = 0.0011$) and cytoplasmic score ($P = 0.0462$) were related to a worse disease-specific survival (DSS) in the entire cohort and in the clinicopathological subgroups
- No significant correlation was found between HMGB1 gene expression and DSS

Conclusions:

- These findings indicate that HMGB1 may be a useful prognostic biomarker in MPM when detected by immunohistochemistry