PULMONARY PATHOLOGY JOURNAL CLUB
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Discussion articles

Bois MC et al. No definite clinical features of immunoglobulin G4-related disease in patients with pulmonary nodular lymphoid hyperplasia. Hum Pathol 2017; 80-6.

Purpose: Investigate the number of IgG4-expressing cells, IgG4 to IgG ratio, and presence of clinical features of IgG4-related disease in pulmonary nodular lymphoid hyperplasia (PNLH). Since EBV-positive cells have also been reported in IgG4-related lymphadenopathy, the presence of EBV is also assessed.

Methods:

- After exclusion criteria applied, 84 surgically resected cases of PNLH reviewed
- Slides evaluated for: 1) confirm diagnosis of PNLH and 2) features suggestive of IgG4-related lung disease (IgG4-RLD)
- Controls: Usual interstitial pneumonia (UIP) with increased lymphoplasmacytic infiltrate (n = 5), randomly selected thoracic lymphadenopathy (n = 2), diffuse lymphoid hyperplasia of the lung without nodularity (n = 2)
- Applied immunohistochemical stains, using antibodies directed against IgG and IgG4
  - 3 "hot spots" manually quantified for both IgG and IgG4, then IgG+/IgG4+ ratio calculated using median absolute counts
- EBV-ISH performed on cases with ≥40 IgG+ cells per HPF
- Clinical parameters: patient demographics, serologies, radiographic findings, and duration of clinical follow-up

Results:

- 26 cases (30%) had both PNLH and at least 1 histologic feature of IgG4-RLD
  - 14 (54%) widespread storiform fibrosis
  - 10 (38%) focal storiform fibrosis
  - 6 (23%) obliterative vascular changes
  - 7 (27%) dense peribronchial inflammation
  - 4 (15.4%) lymphangitic pattern of lymphoplasmacytic inflammation
- Median absolute IgG4+ cell count in PNLH 36 per HPF with median IgG4+/IgG ratio of 0.24
  - Significantly different from thoracic lymphadenopathy (P = .0011), but not significantly different from UIP or diffuse lymphoid hyperplasia
- 3 cases of PNLH showed increased IgG4+ cells (range 55-139) and median IgG4+/IgG+ ratio suggestive of IgG4-RLD
  - 32 y/o woman ultimately diagnosed with undifferentiated connective tissue disease; serum IgG4 level not elevated
  - 12 y/o girl w/ hemoptysis and hilar congenital hemangioma; follow-up N/A
  - 74 y/o man with CML, RA, and smoking, present with 2 nodules (3, 2 cm)
- 1 case diffuse lymphoid hyperplasia suggestive of IgG4-RLD: 70 y/o man with elevated serum RF, treated with prednisone, resulting in clinical resolution of symptoms
- EBV-ISH negative in 10 of 12 cases of PNLH; failed in 2 cases

Take-home message: PNLH does not appear to be a common manifestation of IgG4-RLD (if it is one). EBV infection is not likely to be a common etiology of PNLH.

Ikeda S et al. Abundant immunoglobulin (Ig)G4-positive plasma cells in interstitial pneumonia without extrathoracic lesions of IgG4-related disease: is this findings specific to IgG4-related lung disease? Histopathology 2017; 70: 242-52.

Purpose: Assess whether idiopathic interstitial pneumonias with marked IgG4-positive plasma cell infiltrate represent a separate entity or subtype of IgG4-related lung disease (IgG4-RLD) in patients with no extrathoracic manifestations of IgG4-related disease (IgG4-RD).

Methods:

- Retrospectively reviewed 640 cases of surgical lung for diffuse lung disease from 1/2001 to 3/2013
  - Exclusion criteria: Occupational/Environmental exposures; connective tissue disease; extrathoracic lesions of IgG4-RD
- 18 of remaining 314 cases showed numerous plasma cells, and IgG and IgG4 immunostains applied
- 5 of 18 cases with >50 IgG4+ plasma cells in a HPF and IgG+/IgG4+ ratio of >40%
- Investigated clinical (smoking status, comorbidities, serologies), radiographic, and pathologic features

Results:

- 5 of 5 males; ages 55-78 years (median 72); current/former smokers
- Serum IgG4 elevated in 4 cases; not measured in one case
- HRCT (table 5): ground-glass opacities (5); reticulations (4); lower lobe predominant (5); subpleural distribution (2); traction bronchiectasis (3); honeycombing (2)
- Histology:
  - 4 of 5 cases showed histologic pattern of fibrotic NSIP and/or UIP
  - 1 cellular NSIP
  - All found to have lymphoid follicles
  - 2 cases with obliterative phlebitis
- All patients treated with prednisolone with rapid improvements of serum IgG4 levels and imaging findings
- Compared to the plasma cell-rich IgG4-negative group (13): More females; similar histology; required higher immunosuppression (prednisone + cyclosporine); two developed clinical symptoms of connective tissue disease

Take-home message: The authors conclude that while the patients met diagnostic criteria for IgG4-RD, they cannot conclude that these cases represent IgG4-RLD, since they lack histopathologic features typically associated with this entity and all cases also met criteria for lung-predominant connective tissue disease, favoring instead that these cases represent a new entity.

Li W et al. Combinatorial analysis of FISH and immunohistochemistry reveals rare genomic events in ALK fusion patterns in NSCLC that responds to crizotinib therapy. J Thorac Oncol 2017; 12: 94-101.

Purpose: Explore the complicated rearrangement mechanisms underlying cases with positive ALK by immunohistochemistry with atypical or negative FISH study.

Methods:

- 3128 patients with NSCLC enrolled (from 3/2013 to 1/2016) that did not include any patients receiving neoadjuvant therapy
- Anti-ALK (Ventana-D5F3) antibody applied and FISH analysis performed on all biopsy and resected cases; only FISH performed on cytology preparations (137)
- Targeted NGS performed on cases with positive IHC, but negative/atypical FISH

Results:

- 2991 cases tested by both *ALK* IHC and FISH analysis
  - Overall, 7.3 % (228) ALK IHC positive; 6.8% (214) *ALK* FISH positive
- 11 (0.35%) cases with positive IHC, but negative FISH
  - 8 of 14 cases with *EML4-ALK* rearrangements by NGS
  - 3 cases positive IHC with no *ALK* gene rearrangements by NGS
- 3 (0.1%) cases with positive IHC, but atypical FISH
  - Isolated 5' signals (2) by FISH shown to have novel gene rearrangement partners *BIRC6* and *PICALM*
  - Isolated 3' signal (1) by FISH shown to have novel translocation partner *BCEBPZ*
- 4 of 14 patients treated with crizotinib
  - 3 positive IHC, but no *ALK* gene fusions by NGS
  - 1 positive *EML4-ALK* rearrangements by NGS
  - 100% response rate with disease progression in the *EML4-ALK* rearrangement patient at 13 months, and progression in the *ALK* fusion negative patients at 20.7 months

Take-home message: Although cases of discordant ALK immunohistochemistry and FISH represent less than one percent of cases, these findings suggest that combinatorial assays may be the best approach to identification of patients who may benefit from crizotinib therapy. However, since three patients with over-expression of ALK by immunohistochemistry without confirmed ALK gene fusions benefitted from crizotinib, perhaps we are selecting out patients who might benefit from the drug by relying on molecular studies alone to guide therapy?

Benzerdjeb N et al. GLUT1: A novel tool reflecting proliferative activity of lung neuroendocrine tumors? Pathol Int 2017; 67: 32-6.

Purpose: Assess the utility of the GLUT1 isoform immunostain in the diagnosis of neuroendocrine tumors of the lung.

Methods:

- 36 consecutive cases of surgically biopsies or resected neuroendocrine tumors at University Hospital of Amiens, France
  - 13 cases typical carcinoid tumor
  - 5 cases atypical carcinoid tumor
  - 8 cases small cell carcinoma
  - 10 cases large cell neuroendocrine carcinoma
- GLUT1 expression assessed by immunohistochemistry
- H-score generated by visual estimation by two independent operators
  - H-score = intensity x distribution
  - Intensity: 0 (no staining) to 3 (strong staining)
  - Distribution: Percent staining

Results:

- Carcinoid tumors (18 cases)
  - 1 case showed no staining
  - 16 cases (88.9%) had low staining intensity
  - 1 case had moderate staining intensity
  - All cases with positive staining only showed cytoplasmic staining; no membranous staining
  - H-score (mean ± SD) for typical carcinoid: 1.1 ± 0.3
  - H-score (mean ± SD) for atypical carcinoid: 1.25 ± 0.3
- Neuroendocrine carcinomas (18 cases)
  - 3 cases had low staining intensity
  - 6 cases had moderate staining intensity
  - 9 cases (50.0%) had high staining intensity
  - Of the positive cases, a cytoplasmic and membranous staining pattern was more often observed (87.5% small cell carcinoma; 70% large cell neuroendocrine ca)
  - H-score (mean ± SD) for small cell carcinoma: 2.4 ± 0.7
  - H-score (mean ± SD) for large cell neuroendocrine carcinoma: 2.2 ± 0.9

Take-home message: GLUT1 shows differential expression in carcinoid tumors and neuroendocrine carcinoma; however, it does not provide meaningful differential expression in typical versus atypical carcinoid tumors or small cell carcinoma versus large cell neuroendocrine carcinoma. I wonder about the utility of this stain in surgically resected specimens, since "carcinoid tumor *versus* small cell carcinoma" is usually not the question; rather, this stain might have find a role in the assessment of limited biopsies or liquid biopsies with ambiguous cytologic features.

Articles for notation

Neoplastic lung disease

Detterbeck FC et al. The eighth edition lung cancer stage classification. CHEST 2017; 151: 193-203.

Take-home message: This article summarizes the changes in the 8th ed. of the AJCC/UICC lung cancer stage classification, which became the worldwide standard on January 1, 2017; however, implementation is delayed in the United States. The main change to the TNM staging is now subdivision of the primary tumor (T) in 1 cm increments up to 5 cm, >5 to 7 cm are now T3, and T4 if >7 cm, and the M category now distinguishing solitary and multiple distant metastases. The N category is unchanged.

Fujimoto M et al. Adipophilin expression in lung adenocarcinoma is associated with apocrine-like features and poor clinical prognosis: an immunohistochemical study of 328 cases. Histopathology 2017; 70: 232-41.

Take-home message: This study aimed to investigate adipophilin (ADP), a member of the lipogenic pathway, expression by immunohistochemistry in 328 resected lung adenocarcinomas, and correlate with histologic, molecular, and clinical characteristics. Fifty-one (15.5%) cases showed ADP expression, which ranged from 6 to 50 percent of tumor cells. ADP-positive cases were most commonly solid adenocarcinoma with apocrine-like features, and had significantly more vascular invasion and worse 5-year overall and disease-free survivals; there was no specific molecular mutation associated with ADP expression.

McGowan M et al. PIK3CA mutations as prognostic factor in squamous cell lung carcinoma. Lung Cancer 2017; 103: 52-7.

Take-home message: *PIK3CA* mutations and PD-L1 (which is upregulated by PIK3CA) expression by immunohistochemistry were studied in 308 cases of squamous cell carcinoma in hopes of understanding the prognostic importance. Thirty-five cases (11.4%) harbored *PIK3CA* mutations with most cases showing mutations in the helical domain of exon 9, and of those cases, there was lower, but not statistically significant, expression of PD-L1. Statistical analysis showed that the *PIK3CA*-mutated subset had better overall survival and time to relapse as compared to the wild-type, which potentially might be a consequence of lower PD-L1 expression, resulting in lesser immune-evading capacity.

Mori S et al. High expression of programmed cell death 1 ligand 1 in lung adenocarcinoma is a poor prognostic factor particularly in smokers and wild-type epidermal growth-factor receptor cases. Pathol Int 2017; 67: 37-44.

Take-home message: PD-L1 expression by immunohistochemistry was evaluated in 296 resected adenocarcinomas, and survival assessed with special regard to smoking history and *EGFR* (exon 19) mutation status. A two part scoring system (stain intensity and percentage) was used to stratify patients as "high" or "low" PD-L1 expression with a cut-off score of 50. Patients with high expression of PD-L1 were found to have significantly worse disease-free and overall

survival as compared to those with low expression, particularly in current or former smokers and those with mutant *EGFR*.

Non-neoplastic lung disease

Chilosi M et al. Epithelial to mesenchymal transition-related proteins ZEB1, β-catenin, and β-tubulin-III in idiopathic pulmonary fibrosis. Mod Pathol 2017; 30: 26-38.

Take-home message: The aim of this study was to investigate if Tubβ3, ZEB1, and β-catenin, which are proteins implicated in epithelial to mesenchymal transition (EMT) under the influence of micro-RNAs (miR-200 family), are expressed in 34 cases of usual interstitial pneumonia (UIP; idiopathic pulmonary fibrosis), through the application of immunohistochemistry and confirmatory immunofluorescence assay. All three proteins were expressed in the fibroblastic foci and overlying epithelial cells in 100 percent of UIP cases. These findings suggest that EMT plays a role at the active site of lung architectural remodeling in UIP.

Review articles

Kalhor N et al. Primary salivary gland type tumors of the thymus. Adv Anat Pathol 2017; 24: 15-23.

Take-home message: This is another thymic neoplasm review article from the team at MD Anderson Cancer Center, this time, tackling the ultra-rare primary salivary gland type tumors of the thymus, including malignant (mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma) and benign (mixed tumor, lymphoepithelial sialadenitis, and sabeceous adenoma) tumors. Here, they provide a brief literature review of each tumor's (listed above) clinical presentation, salient histopathologic features, and differential diagnosis. While all of these tumors are very rare, benign tumors are more common in the thymus than malignant ones.

Schlobin OA et al. Pulmonary hypertension in diffuse parenchymal lung diseases. CHEST 2017; 151: 204-14.

Take home message: This is more of a clinically oriented review that touches on many aspects of pulmonary hypertension in diffuse parenchymal lung disease (DPLD), addressing epidemiology, proposed pathogenesis, clinical diagnosis, and treatment. The development and progression of pulmonary hypertension seems to correlate with development of more advanced disease in idiopathic pulmonary fibrosis and sarcoidosis, which represent the bulk of the literature on this subject, with approximately 75 percent of patients suffering from hemodynamic hypertension at the time of transplant. It is unclear whether the development of pulmonary hypertension is an adaptive or maladaptive phenomenon in the context of DPLD, since the pathogenesis is complex and multifactorial, and treatment options limited, at best.

Case reports

Dang J et al. A 54-year-old man with lingual granuloma and multiple pulmonary excavated nodules. CHEST 2017; 151: e13-6.

Take-home message: The patient presented as above, underwent biopsy of a lingual lesion, and was found to have granulomas containing many fungal organisms, morphologically consistent with *Paracoccidiodes brasiliensis* (Paracoccidiomycosis), a diagnosis later confirmed by PCR testing. This organism is endemic to Latin America where the patient had traveled, so do not forget about the "pilot wheel" of budding yeast typical of *P brasiliensis* when presented with a case of granulomatous infection in a world traveler.

Shimizu S et al. A case report of solitary well-differentiated papillary mesothelioma with invasive foci in the pleura. Pathol Int 2017; 67: 45-9.

Take-home message: While undergoing lobectomy for a lung adenocarcinoma, the patient was found to have an incidental 2.9 cm parietal pleural lesion that was diagnosed as well-differentiated papillary mesothelioma (WDPM) with focal invasion into the submesothelial layer. Due to the difficulty in excluding malignant mesothelioma with a "WDPM-like pattern," the patient subsequently underwent extrapleural pneumonectomy, and three years later, although the patient has not suffered recurrence of her WDPM, sadly, she now has widely metastatic lung adenocarcinoma. WDPM with invasive foci is extremely rare and usually multifocal; however, solitary lesions with invasion do reportedly occur.

Letter to the editor

van der Oord K et al. Pleuroparenchymal fibroelastosis with prominent thrombosis. Pathol Int 2017; 67: 56-8.

Take-home message: The patient was a 76-year-old woman that initially presented with shortness of breath, clubbing, crackles, and a restrictive lung disease on PFTs, who subsequently suffered acute hypoxemic respiratory decline and died. At the time of autopsy, she was found to have gross and histologic evidence of pleuroparenchymal fibroelastosis (PPFE) and superimposed "ARDS-like" changes, as well as "multiple small [fibrin] thrombi." The authors speculate that the thrombi might be a "cause of PPFE;" however, as we know, this argument is a difficult one to make in the context of organizing diffuse alveolar damage, which is frequently accompanied by fibrin thrombi.