Pulmonary Pathology Journal Club – (Joanne) ES Yi

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(Joanne) Eunhee S. Yi, MD

Professor of Pathology
Department of Laboratory Medicine & Pathology
Mayo Clinic College of Medicine, Rochester, MN
E-mail: yi.joanne@mayo.edu

Articles for Discussion

Chang JC et al. Bronchiolar adenoma. Expansion of the concept of ciliated muconodular papillary tumors with proposal for revised terminology based on morphologic, immunophenotypic, and genomic analysis of 25 cases. Am J Surg Pathol 2018;42:1010-26

Background

- Ciliated muconodular papillary tumor (CMPT) is a recently described rare tumor with peripheral localization, prominent papillary architecture and three types of cellular components: mucinous, ciliated and basal cells.
- CMPT has shown mutations involving various genes (*BRAF V600E*, *EGFR* exon 19 deletions, *AKT*, *KRAS*, *ALK* rearrangement)
- There may be more cases showing nodular proliferation of bland bi-layered bronchiolar-type epithelium containing a continuous layer of basal cells, similar to CMPT, but not entirely have the features described/proposed for the dx of CMPT
- Concept of adenoma derived from bronchiolar epithelium is not well recognized and they proposed the term "bronchiolar adenoma" (BA) to encompass broader entities that may not meet the strict criteria of CMPT

Methods

- Cases (n=25): prospectively identified during 2016-7 period and through retrospective search of MSKCC archive. 4 cases were from UCLA, Medical College of Wisconsin, Mayo Clinic Arizona, and Fudan University, China (1 case from each place)
- Clinical and radiologic features
- histologic features of resected specimens
- IHC: p40, TTF1 (8G7G3/1), CK5/6, Napsin A, BRAF V600E, ALK (D5F3), CC10 (for clara cells)
- Molecular analysis: 19 of 25 cases underwent NGS or a multigene panel (98-gene, 410-gene, 50-gene or 6-gene panel)

Results

- 25 BAs from 21 patients; 20 wedge resections, 5 lobectomies; 10 patients underwent the procedure solely for BAs, 11 had other lung lesions including primary lung ADC (n=12), metastatic renal cell ca (n=2), and necrotizing granuloma (n=1). 6 BAs were not seen on imaging and incidentally found during pathologic exam grossly (n=2) or microscopically (n=4)
- Of the 12 patients with BA and concurrent lung ADC, 3 had multifocal AAH and AIS
- 3 (14%) had more than 1 BA (2 in 2 pts and 3 in 1 pt)
- BAs tend to be small (range 0.2 – 2.0 cm) with variable TTF1 positivity in the luminal cells and the presence of cilia in the majority of cases. Basal layer cells are positive for basal cell markers (p40, CK5/6)
- Two types:
    - Distal type (68%) resembling morphologic and IHC characteristic of distal respiratory bronchiolar epithelium, many of these contained only focal mucin and/or cilia, partly resemble type II cells or clara cells, may lack ciliated or mucinous cells, TTF1 diffusely positive in both luminal and basal cells
    - Proximal type (32%) recapitulate morphologic and IHC features of proximal bronchiolar epithelium and composed of abundant mucinous and ciliated cells with subjacent basal cells; may show predominantly papillary (with all major diagnostic features of CMPTs; closely mimicking glandular papilloma, except that it is not in endobronchial in location but on alveolar walls) or flat; TTF1 negative in luminal cells of 5 cases
- Comparable mutation profile between CMPT and BAs, supporting their relationship

Take home points

- Beware of the benign peripherally located tumors that can mimic ADC especially on frozen
- Many of these lesions have some but not all morphologic features for CMPT and such cases were proposed to be designated as BA, as a broader term encompassing these tumors & CMPT
- (Don't get confused with "bronchial adenoma" that has been used in the past for carcinoid or salivary-type tumors occurring in the larger airways)
- Needs to be differentiated from frank malignant or premalignant lung lesions as well as other benign conditions such as glandular papilloma that is usually in the central larger airway

Galateau Salle F et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the international mesothelioma panel from the MESOPATH reference center. J Thorac Oncol 2018;13:1189-1203

Background and purpose of study

- Study conducted by the International Mesothelioma Panel (supported by EURACAN and in collaboration with IASLC)
- 2015 WHO categorized MM into epithelioid, biphasic (MM with >10% of epithelioid and sarcomatoid components), and sarcomatoid for prognostic relevance and Tx decisions

- Survival of Biphasic MM (BMM) may correlate with the amount of the sarcomatoid component
- Unclear criteria for sarcomatoid component and interobserver variability between pathologists for identifying this component
- "Transitional" subtype (TMM) (sheets of plump cells starting to lose epithelioid morphology but not overtly spindle shaped and lacking frank sarcomatous features) has not been accepted as a subtype in 2015 WHO but its nature or significance is not entirely clear
- Aims: 1. to evaluate the interobserver agreement in the dx of BMM, 2. to determine the nature and the significance of transitional histologic subtype, 3. to relate the amount/percentage of sarcomatoid component with survival and 4. to evaluate the value of BAP1 IHC and CDKN2A(p16) FISH in assessing stromal component (i.e. for ddx of true sarcomatous vs reactive)

Methods

- Case selection: randomly selected 42 surgical biopsy specimens from the MESOPATH files that have been diagnosed as BMM (total series: 5,219 EMM, 971 BMM, 465 SMM collected over 1/1998-6/2016 period); demographic, clinical, histopathologic, tx and f/u annotations were recorded from the national MESOBANK database
- 14 international pathologists with expertise in MM reviewed the digitally scanned slides (HE and pan-keratin) without knowledge of prior dx or out come
- cases with at least 7 of 14 pathologists recognizing TMM features were selected as a TMM group
- BAP1 loss by IHC and CDKN2A homozygous deletion (HD) by FISH
- Kappa statistics for interobserver agreement and multivariate analysis with Cox regression adjusted for age and gender for survival analysis

Results

- Demographics and Interobserver agreement: mean age 76 yrs, 90% men, asbestos exposure hx 71%; 14 experts provided 544 recorded dx; interobserver correlation was moderate ($w\kappa$=0.45), with agreement in 71% of cases (EMM 17%; SMM 12%)
- Prognosis according to histopathologic grouping: Overall median survival of 42 BMM was 8 mos; 38% at 1 yr, 8% at 2 yrs; significantly different from the EMM and SMM ($p < 0.0001$); OS of BMM was significantly better in cases with <80% sarcomatoid component initially scored by the French panel of experts, with median survival of 12 mos, 56% at 1 yr and 20% at 2 yr; trend of shorter survival ($p=0.08$) in patients with a high-grade spindle cell component
- TMM as a specific clinicopathologic entity: OS curve of the group of sarcomatoid, transitional and pleomorphic MM were very close to each other
- CDKN2A HD by FISH was useful to identify a low-grade spindle cell component as a true sarcomatoid feature in those difficult cases for separating exuberant reactive stromal process from sarcomatoid component of a BMM: 62.5% (5 of 8) of the low-grade spindle cell component of biphasic type, whereas on these cases, BAP1 loss alone on the epithelioid component (4 of 8) or retained (1 of 8) was observed

Take home points

- It may be useful to update definition of BMM that will allow better stratification of patients into risk groups for tx decisions (systemic anticancer therapy vs. surgery vs. palliation only)
- FISH for *CDKN2A*(p16) homozygotic deletion is more useful than BAP1 IHC to determine between benign florid stromal reaction and true sarcomatoid element of BMM on ambiguous spindle cell element in any given case
- "Transitional pattern" is a poor prognostic indicator

Gradecki SE et al. Concordance of PD-L1 expression between core biopsy and resection specimens of non-small cell lung cancer. Am J Surg Pathol 2018;42:1090-4

Background and purpose of study

- PD-L1 expression in NSCLC has been shown to be heterogeneous
- PD-L1 IHC is used to triage Tx for NSCLC pts: ≥50% tumoral staining to be eligible for pembrolizumab as the 1st line Tx; ≥1% as second line Tx following ds progression while receiving 1st line therapies
- Method of tissue sampling has not been established
- This study aimed to determine whether core bx provides sufficient tissue for accurate PD-L1 evaluation

Methods

- Cases: among 608 NSCLC cases resected during 2011-2014 at Univ of Virginia, Charlottesville, 51 cases had core bx with sufficient tissue for further IHC
- Newly stained PD-L1 IHC (SP142) on all cases (n=51) and matching HE reviewed by 1 pathologist
- (SP142 had been previously validated in their lab on a large number of NSCLC cases against results obtained with 22C3 antibody at a referral institution and has shown >95% concordance)
- IHC staining was scored in tumor cells and categorized as <1%, 1-49%, and ≥50%; ≥50% considered positive
- Linear extent of core bx's, greatest linear dimension of resected tumor, interval between bx and resection, and whether or not interval chemotherapy were recorded
- Cohen kappa coefficient of agreement was

Results

- Time interval between bx and resection: 4-133 days (mean 38.73); 3 received chemoradiation; core bx 0.2-2.6cm (mean, 1.14); resected tumor size 0.9-9.6cm (mean 3.29); 25 ADC, 21 SQCC, 5 Adenosqcc
	Resection ≥50%	<50%	
Bx ≥50%	6 (true pos)	2 (false pos)	8 (15.7%)

Bx <50%	2 (false neg) 8 (15.7%)	41 (true neg) 43 (84.3%)	43 (84.3%)

	Resection >50%	1-49%	<1%
Bx ≥50%	6	2	0
1-49%	1	14	1
<1%	1	6	20

- IHC results in core bx and resection were concordant in 92.2% (kappa 0.70; 95% CI 0.43-98) and 76.7% (kappa 0.69; 95% CI, 0.49-0.89) by ≥50% and >1% threshold, respectively
- Sensitivity and specificity in core bx were 75.0% and 95.3%, respectively, by ≥50% criteria
- Sensitivity and specificity in core bx were 76.7% and 95.2%, respectively, by >1% criteria

Take home points

- Detection of tumoral PD-L1 expression in NSCLCs appear largely concordant between core bx's and resection specimens, suggesting that core bx may be adequate for PD-L1 testing
- However, it may be prudent to reassess resection specimens for low-level staining in core bx

Munari E et al. PD-L1 expression heterogeneity in non-small cell lung cancer: defining criteria for harmonization between biopsy specimens and whole sections. J Thorac Oncol 2018;13:113-20

Background and purpose of study

- To better define which value across core bx from the same case more closely reflects the PD-L1 expression status on whole sections and how many core bx specimens are needed for confident classification of tumors in terms of PD-L1 expression

Methods

- Primary NSCLC cases (n=268) who underwent resection at an hospital in Verona, Italy, during 2003-2017 with available sides and PPFE blocks; none had therapy before surgery
- TMA (5 cores, 1mm in diameter, sampled from diverse areas of the tumor randomly numbered from 1 to 5) as surrogate of bx's; 5 cores per case and compared PD-L1 staining (SP263) results with whole tumor sections
- Cores showing a neoplastic component of ≥30% were included (those with <30% were excluded)
- IHC scoring: <1%, 1-49%, ≥50%, by two pathologists; discordant cases were evaluated by a third pathologist
- χ^2 testing to analyze contingency tables and ROC curves were constructed to evaluate the predictive ability of core bx samples for PD-L1 status on whole sections; Cohen's κ was calculated for interrater agreement

Results

- N=268; 183 ADC, 64 SQCC, 21 others (large cell ca, adenosqcc, LCNEC); median size of tumors 2.7 cm (0.8-21cm)
- PD-L1 positive cases: 39% (≥1% cutoff), 10% (≥50% cutoff)
- Interobserver variability and heterogeneity of PD-L1 expression: discrepancy between the two pathologists on whole sections in only 6 cases: in two, lack of concordance at a cutoff 1% and in 4 at cutoff of 50% (kappa 0.98 and 0.91, respectively). after consensus built, one case as negative (<1%) and the other as 1-49%, and the other four as ≥ 50%
- because of lost during processing (n=11), less than 30% of tumor cells (n=72), there were 215 cases with 5 cores, 31 had 4 cores, 16 had 3 cores, 4 had 2 cores, 2 had 1 core available
- on cores, lack of concordance between the two pathologists occurred in 21 cases (kappa 0.92 and 0.82 at cutoffs of 1% and 50%, respectively
- when all cores available for each case were considered, the concordance rates within the 104 cases that showed heterogeneity on whole sections were 93% at a cutoff of 1% and 88% at a cutoff of 50%; discrepancies were due to the heterogeneous expression (Fig 1)
- when they compared the PD-L1 results obtained across tissue cores for each case to establish which value among the maximum, minimum, mean and median showed the highest rate of concordance with that obtained on the basis of whole section, maximum and mean values appeared to better reflect PD-L1 expression on the whole sections. Lowest false negative by maximum value for cutoffs of both 1% and 50%. Maximum value across cores was associated with high concordance between cores and whole sections and the lowest number of false-negative cases overall
- To reach high concordance with whole sections, 4 and 3 cores are necessary at cutoffs of 1% and 50%, respectively

Take home points

- When evaluating multiple bx specimens for PD-L1 assessment, the maximum value across cores was associated with high concordance between cores and whole sections and the lowest number of false-negative cases overall
- To reach high concordance with whole sections, 4 and 3 cores are necessary at cutoffs of 1% and 50%, respectively

Gupta N et al. Smoking-related diffuse cystic lung disease. Chest 2018;154:e31-35

Background

- Cigarette smoking can result in many types of parenchymal lung diseases including diffuse cystic lung diseases (DCLD) that are not very well known
- LAM is the prototypical DCLD with characteristic HRCT findings, which often bypass a confirmatory biopsy

- This study reports 4 cases of smoking related DCLD identified from the cases with presumed dx of LAM

Methods

- Retrospective chart review of 4 pts referred to their institution with DCLD and presumed dx of LAM and underwent surgical lung bx showing smoking-related small airway damage including distal bronchiolectasis with mucostasis, emphysema and cyst formation

Results

- All patients were women, mean age 43.5 years (range 31-53)- *typical demographic for LAM*
- Presenting symptoms: DOE (all 4), chronic cough (2 of 4)
- Active smokers (n=3) with 18 pack years (range 5-32); significant second smoking (n=1)
- Normal alpha 1 antitrypsin level
- None with spontaneous pneumothorax, sicca sx, serologic findings for Sjogren's syndrome, skin lesion, evidence of Birt-Hogg-Dube syndrome, tuberous sclerosis or renal angiomyolipoma
- HRCT: all showed multiple, round, thin-walled cysts of variable sizes distributed diffusely throughout the lung parenchyma; some cysts were perivascular or contained internal structures (septations or blood vessels). Two showed centrilobular emphysema.
- Histopathology: Loss of alveolar density with multiple cystic spaces in all, corresponding to the DCLD on HRCT. Alveolar walls with normal thickness surrounded or traversed the cystic spaces. cystic spaces were associated with small airways, with some of the spaces representing dilated distal bronchioles and alveolar ducts with vessels in many of the walls of the cystic spaces; cyst sizes (2mm – 2 cm); no features of PLCH, LAM on IHC as well as on HE

Take home points

- Smoking-related DCLD may mimic LAM on HRCT, the exact mechanism of which is unclear; internal structures or septations within the cysts should prompt a suspicion for non-LAM etiology and confirmatory bx to be done before launching the sirolimus tx

Articles for Notation

<u>Neoplastic</u>

Dudnik E et al. BRAF mutant lung cancer: Programmed Death Ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. J Thorac Oncol 2018;13:1128-37

Background and purpose of study

- The efficacy of immune check point inhibitors (ICPi) in BRAF mutant NSCLC is unknown

Methods

- Multi-institutional retrospective study from Israel, looking into 39 patients with BRAF mutant NSCLC
- The patients were divided into 2 groups: V600E (group A; n=21) and non-V600E (group B; n=18)
- PD-L1 expression, tumor mutational burden (TMB) and microsatellite instability status were assessed in 29 (74%), 11 (28%) and 12 (31%) patients, respectively
- Objective response rate, progression-free survival (PFS) with ICPi and overall survival (OS) were analyzed

Results

- PD-L1 expression and microsatellite instability:
    - group A: 8 of 19 high (>50%), 6 of 19 intermediate (1-49%) and 5 of 19 no (<1%) PD-L1 expression; high TMB in 2 tumors, none was microsatellite instability high status;
    - group B: 5 of 10 high, 1 of 10 intermediate and 4 of 10 no PD-L1 expression
- ICPi response rate and survival: not affected by BRAF mutation type or PD-L1 expression status
    - group A 25%, median PFS 3.7 months, median OS not reached
    - group B 33%; median PFS 4.1 months

Take home points

- BRAF mutant NSCLC is associated with high level of PD-L1 expression, low/intermediate TMB and microsatellite-stable status
- ICPi have favorable activity both in both group A and B

Millares L et al. Tumor-associated metabolic and inflammatory responses in early stage non-small cell lung cancer: local patterns and prognostic significance. Lung Cancer 2018;122:124-30

Background and purpose of study

- 5-year mortality is >20% even in early stage NSCLC patients treated with surgery
- To identify biomarkers predicting progression and death for closer f/u of the patients at risk

Methods

- A retrospective cohort of early-stage surgically-treated NSCLC patients enrolled for IASLC Staging Project
- TMA constructed with tumor and non-tumor lung tissue to evaluate pentose phosphate pathway proteins, inflammatory markers (COX-2, TNG-α, IL-1β, NFκB-p65 and Ki67) and PD-L1 by IHC

Results

- High IL-1β level in tumor tissue was independently associated with 3-year mortality in NSCLC, mainly in ADC on multivariate cox proportional hazard modeling

Take home points

- Inflammation biomarker may contribute to the identification of patients who are at risk of recurrence and may be candidates for adjuvant therapies

Owen D, et al. Expression patterns, prognostic value and intratumoral heterogeneity of PD-L1 and PD-1 in thymoma and thymic carcinoma. J Thoracic Oncol 2018;13:1204-1212

Background and purpose of study

- expression patterns and prognostic implication of PD-1 and PD-L1 in thymic epithelial tumors (TETs) have shown conflicting results
- intratumoral heterogeneity of PD-1/L1 expression has not been described in TETs

Methods

- retrospective single-center review of 35 resected TET cases (32 thymomas and 3 thymic carcinomas) by IHC with PD-1 (clone NAT105) and PD-L1 (22C3)

Results

- PD-L1 expression in 29 of 35 (83%) TETs: 100% (3 of 3) thymic ca, 81% (26 of 32) thymomas
- PD-1 expression in 27 of 35 (77%) TETs: 33% (1of 3) thymic ca, 81% (26 of 32) thymomas
- High PD-1 expression was associated with lower-grade tumors
- PD-L1 expression was not associated with higher grade tumors or higher stage
- Neither PD-L1 nor PD-1 expression was significantly associated with survival
- 3 thymoma cases with multiple available sections for PD-1/L1 expression showed differing expression patterns of both PD-L1 and PD-1 in 2 patients

Take home points

- High expression of PD-L1 and PD-1 in TET and intratumoral heterogeneity of PD-L1 and PD-1 in thymoma patients

Okiror L et al. Prognostic factors including lymphovascular invasion on survival for resected non-small cell lung cancer. J Thorac Cardio Surg 2018;156:785-93

Background and purpose of study

- A retrospective observational study on the influence of tumor LVI on OS in resected NSCLC and other prognostic factors for survival

Methods

- 524 patients who had surgical resection of NSCLC in a single institution over a 3 year period

Results

- 225 (43%) had tumors with LVI; patients with LVI showed lower OS ($p < .0001$) and LVI was independently associated with visceral pleural involvement ($p < .0001$). In multivariate model, LVI (HR 2.58; 95% CI 1.63-4.09; $p< .0001$) was an independent worse prognostic factor, along with parietal pleural invasion, advanced age, and N2 LN involvement

Take home points

- LVI is associated with a worse OS in patents with resected non-small cell ca regardless of tumor stage
- Parietal pleural involvement, N2 nodal status and advanced age independently predict poor OS

Chen L et al. Clinical significance of FAP-α on microvessel and lymphatic vessel density in squamous cell carcinoma. J Clin Pathol 2018;71:721-8

Background and purpose of study

- Role of cancer-associated fibroblasts (CAFs) has been recognized in cancer progression but identification of relevant active CAFs has been difficult
- angiogenesis and lymphangiogenesis are essential for tumor growth and metastasis, and microvessel density (MVD) and lymphatic vessel density (LVD) have been accepted as predictors of metastasis and progression of disease
- To determine the association between CAFs and MVD/LVD

Methods

- 122 samples from lung resection performed in a single institution (2011-14)
- IHC for MVD, LVD, CAF (by fibroblast activation protein α or FAP-α)

Results

- High stromal CAF abundance correlated with increased MVD and LVD in lung Sqcc ($p<0.05$).
- χ^2 test revealed significant association of higher CAF density and LN metastasis with worse survival

Take home points

- CAF density, shown by FAP-α staining pattern, was a worse prognostic marker in lung Sqcc

Toth LN et al. Non-small cell lung cancers with isocitrate dehydrogenase 1 or 2 (IDH1/2) mutations. Hum Pathol 2018;78:138-43

Background and purpose of study

- IDH1/2, metabolic enzymes, convert isocitrate to α-ketoglutrate, and *IDH1/2* mutations are associated with multiple malignancies including gliomas
- To examine the prevalence and features of NSCLC with *IDH1/2* mutations

Methods

- 800 lung cancer samples (5/2013-3/2017) were sequenced for somatic mutations of *IDH1/2*

Results

- 9 samples (1.1%) from 8 patients harbored an *IDH1* or *IDH2* mutations
- All positive cases were ADC and all patients had a smoking hx
- 88% of patients' tumors had a coexisting KRAS mutation and
- 6 of 8 patients were >70 years; significantly older than *KRAS*-mutated NSCLC with hx of smoking
- 5 patients had stage IV ds and 3 had stage I ds

Take home points

- *IDH1/2* mutants may define a distinct subset of KRAS mutant lung cancers
- Further study is needed to determine eligibility and response to IDH2 inhibitor enasidenib

Donner I et al. Germline mutations in young non-smoking women with lung adenocarcinoma. Lung Cancer 2018;122:76-82

Background and purpose of study

- Considerable number lung cancer patients are never smokers, who are mainly women
- Population-based sampling of young patients to discover candidate predisposition variants for lung ADC in never-smoking women

Methods

- Archival normal tissue materials from 21 never-smoker women who had been diagnosed with lung ADC before the age of 45, and exome sequence their germline DNA

Results

- Potentially pathogenic variants were found in 8 Cancer Gene Census germline genes: *BRCA1, BRCA2, ERCC4, EXT1, HNF1A, PTCH1, SMARCB1* and *TP53*
- The variants in *TP53, BRCA1* and *BRCA2* are likely to have contributed to the early onset lung cancer in the respective patients (3/21; 14%)

Take home points

- Lung ADC can be a component of certain cancer predisposition syndromes

Lissa D et al. HOXA9 methylation and blood vessel invasion in FFPE tissues for prognostic stratification of stage I lung adenocarcinoma patients. Lung Cancer 2018;122:151-9

Background and purpose of study

- Third of stage I lung ADC patients who underwent surgery with curative intent have recurrence
- Prognostic biomarkers are needed to tailor postoperative management
- To evaluate the utility of Homeobox A9 (HOXA9) promoter methylation, alone or in combination with blood vessel invasion (BVI) assessment, for prognostic significance of stage I lung ADC pts

Methods

- Droplet digital PCR (ddPCR) to measure HOXA9 promoter methylation in FFPE
- Prognostic value of HOXA9 promoter methylation and BVI, alone and in combination was evaluated by K-M survival and Cox regression analyses in a cohort of 177 stage I lung ADC patients from the NCI-MD study

Results

- ddPCR assay detected as low as 0.1% methylated DNA input
- high methylation was independently associated with worse cancer-specific survival and identified high-risk stage 1A and 1B patients, in multivariate model
- high methylation tumors showed high frequency of TP53 mutations and other molecular markers associated with aggressive behavior
- combination with BVI also identified high-risk patients

Take home points

- ddPCR technique worked to measure HOXA9 promoter methylation in FFPE samples
- alone or combined with BVI in a prognostic classifier, HOXA9 promoter methylation could be potential biomarker to guide the early stage lung ADC after surgery

Li Y et al. Identification of MET exon14 skipping by targeted DNA- and RNA-based next-generation sequencing in pulmonary sarcomatoid carcinomas. Lung Cancer 2018;122:113-9

Background and purpose of study

- pulmonary sarcomatoid ca (PSC) comprises a heterogeneous group of NSCLCs, with poor px even after aggressive tx. MET exon 14 skipping in PSC can be a target for MET TKIs

Methods

- 77 PSC cases were tested for driver mutation profile including MET exon 14 alterations by targeted DNA and RNA based NGS
- they also studied demographic features and clinical outcomes of patients harboring MET exon 14 skipping mutation in their tumors

Results

- 20.8% of PSC patients harbored MET exon 14 skipping; one case had concurrent KRAS mutation
- DNA and RNA based NGS showed concordant results, but RNA sequencing was more accurate
- those with MET exon 14 skipping were older and had shorter DFS

Take home points

- given the worse px with MET exon 14 skipping and emerging effect tx with MET TKI, clinical screening of MET exon 14 skipping in PSC might be helpful

Kwon D et al. Overexpression of endoplasmic reticulum stress-related proteins, XBP1s and GRP78, predicts poor prognosis in pulmonary adenocarcinoma. Lung Cancer 2018;122:131-7

Background and purpose of study

- Endoplasmic reticulum (ER) stress is associated with tumor development and progression
- They explored clinicopathologic implication of ER stress in NSCLC

Methods

- Expression of two ER stress-related proteins, GRP78 and XBP1 spliced-form (XBP1s) was evaluated in 369 ADCs and 246 Sacs of the lung by IHC

Results

- Both proteins were expressed in high level in ADCs and SqCCs
- In ADCs, XBP1s expression was higher in pts with ALK translocation than in those with wild-type ALK or EGFR mutation ($p<0.005$)
- no significant difference in GRP78 expression according to ALK or EGFR status
- High expression of XBP1 or GRP78 was an independent poor prognostic factor in ADCs

Take home points

- XBP1 or GRP78 are expressed variably in ADC of the lung, and their overexpression is associated with poor px
- The ER stress pathway may be a prognostic biomarker and potential therapeutic target for ADC

Sun F et al. Ground glass opacities: imaging , pathology, and gene mutations. J Thorac Cardiovasc Surg 2018156;808-13

Background and purpose of study

- To correlate between CT characteristics, pathologic subtype, and gene mutation associated with GGO to guide the treatment of lung ADC

Methods

- Retrospective study of patients with GGO on CT who underwent surgery in one institution (2013-6)
- GGO divided into two groups: 1. <20mm in diameter, <50% solid component; 2. ≥20mm or ≥50% solid component
- differences in pathologic subtype an gene mutation pattern between the two groups were compared using χ^2 test
- correlation between pathologic subtype and EGFR mutation status was also tested using χ^2 test

Results

- a total of 1,018 cases (408 group 1, 610 group 2); 544 were tested for EGFR gene mutation
- group 1 and 2 differed in predominant subtype and all included subtype; 57 of 59 micropapillary or solid type belonged to group 2
- EGFR gene mutation rate was significantly higher in group 2, and correlated with pathologic subtype (lowest in AIS, highest in papillary type
- EGFR mutation subtype did not differ between the groups

Take home points

- CT characteristics of GGO correlated with pathologic subtype and gene mutation rate
- EGFR mutation rate differed significantly among pathologic subtypes
- Group 1 (<20mm, solid <50%) seldom contain subtypes with poor px (micropapillary or solid) and EGFR mutations rate was significantly lower

Fang W et al. Lymph node metastasis in thymic malignancies: a Chinese multicenter prospective observational study. J throac Cardiovasc Surg 2018;156:824-33

Background and purpose of study

- To study the incidence and pattern of LN metastases in thymic malignancies

Methods

- a multicenter prospective observational trial with intentional LN dissection by Chinese Alliance for Research in Thymomas (ChART) and compared with their prior ChART retrospective study
- included thymic tumors without pretreatment

Results

- n=275 cases; metastasis was found in 41 nodes (3.04%) in 15 patients (5.5%); 2.1% (5 of 238) in thymomas, 25% (6 of 24) thymic carcinomas, and 50% (4 of 8) neuroendocrine tumors
- T1, 2.7% (6/222); T2, 7.7% (1/13); T3, 18.4% (7/38); T4, 50% (1/2)
- Nodal involvement was higher compared with their ChART retrospective study (5.5% vs. 2.2%), though the two groups were comparable in tumor stage and histology

- N1 nodes in 13 pt (86.7%), N2 nodes in 8 patients (53.3%); 6 (40%) had simultaneous N1 and N2 metastasis; 6 (40%) had multistation nodal disease
- Low risk group (T1-2; type A-B2) had 0.5% (1/192) and high risk group (T3-4; type B3 and above) had 16.9% (14/83) nodal metastasis
- On multivariate analysis, type B3/thymic ca/neuroendocrine tumors, category T3 or above, and N2 dissection predicted a greater likelihood of finding nodal metastasis

Take home points

- LN metastasis in thymic malignancies is more common than previously recognized especially in tumors with aggressive histology and advanced T category
- Intentional LN dissection increases the detection of nodal involvement and improves accuracy of staging
- In selected high-risk patients, systemic dissection of both N1 and N2 nodes should be considered for accurate tumor staging

<u>Non-neoplastic</u>

Sarmiento E et al. Monitoring of early humoral immunity to identify lung recipients at risk for development of serious infections: a multicenter prospective study. J Heart Lung Transplant 2018;37:1001-12

Background and purpose of study

- A multicenter study to assess monitoring of early humoral immunity as a means of identifying lung recipients at risk of serious infections

Methods

- 82 adult lung recipients at 5 centers in Spain were prospectively analyzed
- Data collection before transplantation and at 7 and 30 days after transplantation
- Biomarkers tested: IgG, M, A, C3, C4, titers of Ab's to pneumoccocal polysaccharide antigens (IgG, IgA, and IgM) and Ab's to CMV (IgG) and serum B-cell activating factor (BAFF) levels
- Clinical f/u for 6 months: for bacterial infections requiring iv anti-microbial agents, CMV disease, and fungal infections requiring therapy

Results

- 33 patients (40.2%) developed at least 1 serious bacterial infections, 8 (9.8%) had CMV disease, and 10 (12.2%) ha fungal infections
- Lower IgM Ab level against pneumococcal polysaccharide antigens at day 7 (<5mg/dl) were a risk factor for serious bacterial infection (adjusted odds ratio 3.96; p=0.0099). at day 7, IgG hypogammaglobulinemia (<600 mg/dl) was associated with a higher risk of CMV ds (after adjustment for CMV mismatch odds ratio 8.15; p=0.028) and fungal infection (adjusted odds

ratio 8.03; p=0.015). Higher BAFF levels before transplantation were associated with a higher rate of developing serious bacterial infection and acute cellular rejection

Take home points

- Early monitoring of specific humoral immunity parameters proved useful for the identification of lung recipients at risk of serious infections

Reviews, Editorials, Letters, etc

Kumar A et al. Current concepts in pathogenesis, diagnosis, and management of smoking-related interstitial lung diseases. Chest 2018;154:394-408

Take home points

- Useful reference regarding smoking related ILD from authors at U of Michigan and Mayo Clinic Rochester
- This review covers not only well recognized spectrum of smoking-related interstitial diseases including RB-ILD, DIP and PLCH but also less well known conditions such as SRIF and acute eosinophilic pneumonia, along with other diseases that have loose association with smoking, including IPF and CPFE. The impact of smoking in a various types of connective tissue disease-ILD is also discussed.

Yi et al. Updates on selected topics in lung cancers. Air space invasion in adenocarcinoma and Ki-67 staining in carcinoid tumors. Arch Pathol Lab Med 2018;142:947-51

Take home points

- A concise review on the two topics that have been challenging pulmonary pathologists and general surgical pathologists alike

Gkiozos I et al. Sarcoidosis-like reactions induced by checkpoint inhibitors. J Thorac Oncol 2018;13:1076-82

Take home points

- Data regarding immune checkpoint inhibitor (ICI)-induced sarcoidosis-like reaction in the literature
- 3 classes of ICIs have been implicated: anti-cytotoxic T-lymphocyte associated protein 4 antibodies, PD1 inhibitors, and PD-L1 inhibitors
- findings are indistinguishable from sarcoidosis with a similar histology, pattern of organ involvement and pattern of clinical manifestations
- the most common locations: thoracic organs(lung and/or mediastinal LNs) and skin

- median time between initiation of an ICI and the development of sarcoidosis like reaction averaged 14 weeks
- clinicians used corticosteroids and/or discontinuing ICI, or take no action
- regardless of clinical intervention, these reactions have uniformly improved or resolved after ICI-tx, which provides additional temporal evidence supporting the presence of a sarcoidosis-like reaction as opposed to real sarcoidosis

Case Reports

Takahashi N et al. Goodpasture's disease in a patient with advanced lung cancer treated with nivolumab: An autopsy case report. Lung Cancer 2018;122:22-24

Take home points

A fatal complication of nivolumab used as second line therapy for NSCLC in a 74 year-old Japanese man; we may see more of these cases unfortunately.

Hodges K eta l. Pleural myopericytoma: A rare neoplasm in a difficult location. J Thorac Cadiovasc Surg 2018;156:e129-e131

Take home points

I never heard of this entity before either in the lung and pleura or any other site. The microscopic finding illustrated in the figure looked quite peculiar.

Ahmed T et al. Non-small cell lung cancer transdifferentiation into small cell lung cancer: A case series. Lung Cancer 2018;122:220-3

Take home points

Actually, it was a series of 46 cases (30 adenoca, 16 sqcc). (502 of 23,015) consecutive lung cancer cases during the study period (from 1/2003 to 1/2015) had had dx both SCLC and NSCLC. Among these 502 cases, 46 cases (30 adenoca, 16 sqcc) met their criteria for transdifferentiation (0.2 %): SCLC occurring within 2 years after a dx of NSCLC. 27 of 30 ADC and 12 of 16 SQCC developed SCLC at the same locations. They suggested that the discovery of SCLC histology after tx of NSCLC may be more common than thought. This study did not address the issue of combined small cell ca, however.

Koba H et al. Next-generation sequencing analysis identifies genomic alterations in pathological morphologies: A case of pulmonary carcinosarcoma harboring EGFR mutations. Lung Cancer 2018;122:146-50

Take home points

A case of pulmonary carcinosarcoma harboring EGFR mutation by a comprehensive NGS