Articles for Discussion


Page 8  Chang SY, Keogh KA, Lewis JE, Ryu JH, Cornell LD, Garrity JA, and Yi ES. IgG4-positive plasma cells in granulomatosis with polyangiitis (Wegener's): A clinicopathologic and immunohistochemical study on 43 granulomatosis with polyangiitis and 20 control cases. Hum Pathol 2013; 44: 2432–2437.


Articles for Notation

Original Articles: Neoplastic


Original Articles: Non-Neoplastic

Shino MY, et al. CXCR3 ligands are associated with the continuum of diffuse alveolar damage to chronic lung allograft dysfunction. Am J Respir Crit Care Med 2013; 188: 1117–1125.

Editorial


Case Reports


Articles for Discussion


Background:
- T1 (≤3 cm) tumors with visceral pleural invasion (VPI) are upstaged to T2a (stage IB) in the TNM classification.

Purpose:
- To investigate the effect of VPI on the cumulative incidence of recurrence (CIR) and overall survival (OS) of lung adenocarcinoma (ADC) ≤2 cm (T1a) and 2 to 3 cm (T1b).

Methods:
- 777 patients with node-negative lung ADC ≤3 cm who underwent resection.

Results:
- Among patients with tumors ≤2 cm, VPI was not associated with either decreased OS or increased CIR (Fig. 2. A & B).
- Among patients with tumors 2 to 3 cm in size, the presence of VPI was associated with decreased OS or increased CIR (Fig. 2. A & B).
- When stage I lung ADCs ≤3 cm were regrouped as either new stage IA (≤2 cm with or without VPI, 2-3 cm without VPI) or new stage IB (2-3 cm with VPI) (Table 3), there was a statistically significant difference in 5-year CIR and OS between new stage IA and new stage IB tumors (Fig. 2. C & D).
Conclusions:

- VPI stratifies prognosis in patients with lung ADC 2 to 3 cm but not in those with tumors ≤2 cm.
- The proposed regrouping of a new stage IB better stratifies patients with poor prognosis, similar to published outcomes in patients with stage II disease, who may benefit from adjuvant chemotherapy.

Background:
- The National Lung Screening Trial (NLST), which compared lung cancer screening with low-dose computed tomography (LDCT) versus chest radiography (CXR), demonstrated a statistically significant mortality benefit of LDCT screening.

Purpose:
- To perform a post hoc analysis to examine whether the benefit was affected by age, sex, smoking status, and tumor histology.

Methods:
- Lung cancer death rates were computed as events over person-years of observation; the mortality risk ratio (RR) was defined as the lung cancer death rate in the LDCT versus CXR trial arms.

Results:
- The overall mortality RR was 0.92 in men and 0.73 in women, with a P value for interaction of .08. RRs were similar for individuals aged <65 years versus those aged <65 years (0.82 vs 0.87), and for current versus former smokers (0.81 vs 0.91).
- By tumor histology, mortality RRs were 0.75 for adenocarcinoma, 0.71 for all non-small cell lung cancers except squamous, 1.23 for squamous cell carcinoma, and 0.90 for small cell carcinoma.
- (RRs were similar for men and women for nonsquamous non-small cell lung cancers (0.71 and 0.70, respectively); women were found to have lower RRs for small cell and squamous cell carcinoma.)

Conclusions:
- A benefit of LDCT did not appear to vary substantially by age or smoking status; (there was weak evidence of a differential benefit by sex).
- A differential benefit across lung cancer histologies may exist.

Background:
- Lipomatous tumors rarely involve the bronchial tree, and detailed morphologic and molecular cytogenetic analysis is lacking.

Methods:
- 12 endobronchial lipomatous neoplasms were studied.
- FISH was performed in subsets of cases for
  - CPM (amplified in atypical lipomatous tumors/well-differentiated liposarcomas [ALT/WDL]), and
  - HMGA1 and HMGA2 (often rearranged in lipomas).

Results:
- The cases occurred predominately in older men (91%).
- Most patients (80%) had a former or current history of heavy smoking.
- Three patients had concurrent pulmonary squamous cell carcinoma, and 1 had a history of multiple lung cancers.
- Most lesions were small (<2.5 cm) and discovered incidentally.
- A subset of tumors showed atypical morphologic features that would be suggestive of ALT/WDL in soft tissue sites, including regions of fibrosis and scattered hyperchromatic stromal cells.
- All cases with atypia were CPM negative and behaved in a clinically benign manner.
- Seven cases were tested for HMGA1 and HMGA2 rearrangement;
  - 4 showed HMGA2 rearrangement, and
  - 1 showed HMGA1 rearrangement, consistent with lipomas.
  - Two cases were negative for HMGA1/2 rearrangements.

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<th>Smoking (Pack-Years)</th>
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<th>Size (cm)</th>
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<th>HMGA1 FISH</th>
<th>Follow-up (mo)</th>
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<td>HMGA2 ANED</td>
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TABLE 1. Clinicopathologic Features of 12 Cases of Endobronchial Lipoma

ANED indicates alive no evidence of disease; BI, bronchus intermedius; ca, carcinoma; DOC, dead of other causes; F, female; LLL, left lower lobe; M, male; NA, not applicable; Neg, negative; RLL, right lower lobe; RUL, right upper lobe.
Conclusions:

- Endobronchial lipomatous neoplasms represent lipomas, even in the presence of morphologic features suggestive of ALT/WDL.
- FISH testing may be very valuable in the analysis of these rare tumors, as true ALT/WDL seem to be very rare or nonexistent at this anatomic site.
Chang SY, Keogh KA, Lewis JE, Ryu JH, Cornell LD, Garrity JA, and Yi ES. IgG4-positive plasma cells in granulomatosis with polyangiitis (Wegener's): A clinicopathologic and immunohistochemical study on 43 granulomatosis with polyangiitis and 20 control cases. Hum Pathol 2013; 44: 2432–2437.

Background:
- Granulomatosis with polyangiitis (GPA) (Wegener's) may mimic IgG4-related disease (IgG4-RD).
- IgG4 immunostaining is often performed in this context for differential diagnosis with IgG4-RD.
- The appropriate cutoff for the number of IgG4+ plasma cells has been proposed in different organs, although it is still not well established.
  - Kamisawa et al and Zhang et al used in their studies a cutoff point of greater than 30 per HPF,
  - Whereas Deshpande et al and Dhall et al used greater than 50 HPF and have reached high sensitivity and specificity in diagnosing autoimmune pancreatitis.

Methods:
- 43 cases of GPA including 26 previously published cases.
  - Sinonasal mucosa/oral cavity/nasopharynx (n = 14)
  - Orbit/periorbital tissue (n = 7)
  - Lung/pleura (n = 14)
  - Kidney (n = 4)
  - Skin (n =3)
  - Dura (n = 1)
- 20 control cases without any clinical evidence of GPA or IgG4-RD
  - Chalazion (n = 8)
  - Chronic sinusitis (n = 8)
  - Chronic tonsillitis (n = 4)

Results:
- Of 43 biopsies, 8 (18.6%) revealed increased IgG4+ cells (>30 per high-power field and >40% in IgG4+/IgG+ ratio) and originated from
  - Sinonasal (n = 4) or
  - Orbital/periorbital (n = 4) regions.
- None of the control cases had increased IgG4+ cells.

Conclusion:
- Increased IgG4+ cells can be seen in sinonasal or orbital/periorbital biopsies of GPA, which could pose as a pitfall in the diagnosis of IgG4-RD.
- However, GPA in other organs and controls did not show increased IgG4+ cells when using the above threshold.
- The biologic or clinical importance of increased IgG4+ cells in GPA cases involving head and neck region is uncertain.

Background:

- The 1999 American Thoracic Society/European Respiratory Society statement on sarcoidosis required that the diagnosis of sarcoidosis be confirmed by a compatible clinical picture, the histological identification of noncaseating granulomas and the exclusion of other diseases capable of producing a similar histological or clinical picture (Am J Respir Crit Care Med 1999; 160: 736–765).
- The traditional approach to confirming the diagnosis of sarcoidosis has presumed histology to be the gold standard.
- Recent studies concluded that endobronchial ultrasound-guided transbronchial needle aspirates (EBUS-TBNA) in combination with transbronchial lung biopsy (TBLB) and endobronchial biopsy (EBB) optimizes the diagnostic yield and should be considered the first-line investigation in patients with suspected sarcoidosis.
- Rapid on-site evaluation (ROSE) of cytological material assists the EBUS-TBNA procedure by informing the bronchoscopist whether TBLB and EBB need to be undertaken.

Purpose:

- This study is the first prospective, blinded study to assess the diagnostic accuracy of EBUS-TBNA with ROSE in patients with suspected sarcoidosis.

Methods:

- Prospective two-center (St Vincent’s Hospital [Sydney, Australia] and the Royal Brisbane Hospital [Brisbane, Australia]) study performed EBUS-TBNA with ROSE followed by TBLB and EBB.
- The diagnostic accuracy of EBUS-TBNA with ROSE was compared to the final cytological assessment and to TBLB and EBB.
Results:
- 60 cases of sarcoidosis.
- ROSE sensitivity was 87.8% (specificity 91%, positive predictive value 97.7%).
- ROSE slide interpretation in combination with the final fixed slide and cell block preparations had a sensitivity of 91.8% (specificity 100%, positive predictive value 100%).
- 67% of patients were confirmed as having sarcoidosis on TBLB and 29% on EBB.
- Interobserver agreement between cytotechnologists and pathologists was very good ($\kappa=0.91$, 95% CI 0.80–1.0 and $\kappa=0.91$, 95% CI 0.79–1.0, respectively).

Conclusions:
- EBUS-TBNA with ROSE has high diagnostic accuracy and interobserver agreement and informs the bronchoscopist whether additional diagnostic procedures need to be undertaken.
- EBUS-TBNA with ROSE should therefore be considered as the first-line investigation of sarcoidosis.
**Articles for Notation**

*Original Articles: Neoplastic*


**Background:**
- Lung cancer, including lung adenocarcinoma, is a heterogeneous disease, which evolves from molecular alterations in the airway epithelium.

**Purpose:**
- To explore whether a subtype of lung adenocarcinomas expresses the unique molecular features of human airway basal cells (BCs), and how expression of the airway BC features correlates with the molecular, pathological and clinical phenotype of lung adenocarcinoma.

**Methods:**
- Three independent lung adenocarcinoma data sets were analyzed for expression of genes that constitute the airway BC signature.
- Expression of the BC signature in lung adenocarcinoma was then correlated to clinical and biological parameters.

**Results:**
- Remarkable enrichment of airway BC signature genes was found in lung adenocarcinomas.
- A subset of lung adenocarcinomas (BC-high adenocarcinoma) exhibited high expression of BC signature genes in association with
  - Poorer tumor grade,
  - Higher frequency of vascular invasion and
  - Shorter survival.
- At the molecular level, BC-high adenocarcinomas displayed
  - A higher frequency of KRAS mutations,
  - Activation of transcriptional networks and pathways related to cell cycle,
  - Extracellular matrix organization, and
  - A distinct differentiation pattern with suppression of ciliated and exocrine bronchiolar cell (Clara cell)-related genes.

**Conclusions:**
- Activation of the airway BC program is a molecular feature of a distinct, aggressive subtype of lung adenocarcinoma.


**Purpose:**
- Patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) respond to ALK inhibitors.
Clinically, the presence of ≥15% cells with rearrangements identified on break-apart fluorescence in situ hybridization (FISH) classifies tumors as positive. Increases in native and rearranged ALK copy number also occur.

**Methods:**
- Specimens
  - 1426 NSCLC clinical specimens
    - 174 ALK-positive
    - 1252 ALK-negative
  - 24 ALK-negative NSCLC cell lines
- ALK copy number and genomic status were assessed by FISH.

**Results:**
- Clinical specimens with 0% to 9%, 10% to 15%, 16% to 30%, 31% to 50%, and >50% ALK-positive cells were identified in 79.3%, 8.5%, 1.4%, 2.7%, and 8.1%, respectively.
- An increased native ALK copy number (≥3 copies per cell in ≥40% of cells) was detected in 19% of ALK-positive tumors and in 62% of ALK-negative tumors.
- In ALK-negative tumors, abundant, focal amplification of native ALK was rare (0.8%).
- Other atypical patterns occurred in approximately 6% of tumors.
- The mean native ALK copy number ranged from 2.1 to 6.9 copies in cell lines and was not correlated with crizotinib sensitivity.
- Neither native or rearranged ALK copy number nor the percentage of positive cells correlated with extra-central nervous system progression-free survival in ALK-positive patients who were receiving crizotinib.

**Conclusions:**
- Overall, 8.5% of tumors fell below the established positivity threshold by ≤5%; further investigation of ALK by other diagnostic techniques in such cases may be warranted.
- Native ALK copy number increases alone were not associated with sensitivity to ALK inhibition in vitro.
- However, rare, complex patterns of increased native ALK in patients should be studied further, because, otherwise, atypical rearrangements contained within these may be missed.


**Background:**
- Currently, fluorescent in situ hybridization (FISH) is considered to be the standard method for assessing formalin-fixed and paraffin-embedded tissue for ALK inversions and translocations.
- However, FISH requires specialized equipment, the signals fade rapidly and it is difficult to detect overall morphology and tumor heterogeneity.
Chromogenic in situ hybridization (CISH) has been successfully introduced as an alternative test for the detection of several genetic aberrations.

**Purpose:**
- To validate a newly developed ALK CISH assay by comparing FISH and CISH signal patterns in lung cancer samples with and without ALK rearrangements.

**Methods:**
- One hundred adenocarcinomas of the lung were included in this study, among them 17 with known ALK rearrangement.
- FISH and CISH were carried out and evaluated according to the manufacturers’ recommendations.
- For both assays, tumors were considered positive if ≥15% of tumor cells showed either isolated 3’ signals or break-apart patterns or a combination of both.

**Results:**
- Red, green and fusion CISH signals were clear-cut and different signal patterns were easily recognized.
- The percentage of aberrant tumor cells was statistically highly correlated between FISH CISH.
- On the basis of 86 samples that were evaluable by ALK CISH, the authors found a 100% sensitivity and 100% specificity of this assay.

**Conclusions:**
- CISH is a highly reliable, sensitive and specific method for the detection of ALK gene rearrangements in pulmonary adenocarcinomas.
- The results suggest that CISH might serve as a suitable alternative to FISH, which is the current gold standard.


**Background:**
- The diagnostic entity of clear cell carcinoma of the lung (CCCL) is controversial, with many investigators arguing against its inclusion in the World Health Organization classification of lung carcinoma.

**Purpose:**
- To study 3 groups of carcinomas with immunohistochemical and molecular assays.

**Material:**
- 6 cases of CCCL
- 7 cases of adenocarcinoma with clear cell change,
- 11 cases of squamous cell carcinoma with prominent clear cell change

**Results:**
- CCCL tended to be present in older individuals with an adenocarcinoma immunophenotype (cytokeratin 7 and TTF-1 positivity).
- Molecular analysis by Sanger sequencing revealed KRAS mutations in 5 of 6 cases of CCCL, 2 of 7 adenocarcinomas with clear cell change, and 2 of 11 squamous cell carcinomas with clear cell change.
Conclusions:
- Although perhaps not a distinct pathologic entity, in this pilot study, CCCL has an immunophenotype similar to solid-type adenocarcinoma with clear cell change and displays more frequent and unusual KRAS mutations than expected in most adenocarcinomas of the lung.


Purpose:
- To evaluate the prognostic value of E-cadherin, β-catenin, vimentin and S100A4 expression in a cohort of squamous cell lung carcinoma (SqCC) patients.

Methods:
- 204 cases surgically resected SqCC.
- Immunohistochemical analyses of
  - E-cadherin
  - β-catenin
  - Vimentin
  - S100A4
- Correlations between the expression of these markers and clinicopathological parameters were analysed using the χ2 test.
- The prognostic value of these markers was evaluated using univariate Kaplan–Meier survival analyses and multivariate Cox proportional hazards model analyses.

Results:
- Significant associations between E-cadherin expression and T stage, histological differentiation, lymph node metastasis, and recurrence were identified.
- Decreased β-catenin expression was significantly correlated with T stage and lymph node metastasis.
- Vimentin expression was associated with histological differentiation and lymph node metastasis.
- Significant correlations were observed between S100A4 expression and lymph node metastasis and recurrence.
- In the univariate analyses, high E-cadherin expression was a positive indicator for overall survival (OS) and disease-free survival (DFS), whereas high S100A4 or vimentin expression was negative indicators for OS and DFS.
- In the multivariate analyses, E-cadherin and S100A4 expression were independent prognostic factors for OS and DFS.

Conclusions:
- Analysis of E-cadherin and S100A4 expression may allow for the identification of patients who are at a high risk of recurrence and poor prognosis in SqCC.

Purpose:
- To evaluate the prevalence of PBK/TOPK (PDZ-binding kinase/T-LAK cell-originated protein kinase) expression and to explore the prognostic significance of PBK/TOPK expression alone and in combination with Ki67 and p53 expression in non-small-cell lung cancer (NSCLC).

Methods:
- The authors detected PBK/TOPK expression in 30 samples of normal lung tissue, 32 lymph node metastases and 279 primary non-small-cell lung cancers by immunohistochemistry, and analyzed the correlation of PBK/TOPK expression with Ki67 and p53 expression in primary tumor tissues.

Results:
- The results showed that PBK/TOPK expression was higher in lymph node metastases (75%) than in primary tumors (44.8%) and normal lung tissues (0%).
- PBK/TOPK expression was associated with histological type, lymph node metastasis, and TNM stage, and was positively correlated with Ki67 and p53 expression in NSCLC.
- Univariate and multivariate survival analyses showed that PBK/TOPK expression was significantly associated with an unfavorable prognosis in NSCLC.
- The prognosis of patients with tumors positive for both PBK/TOPK expression and Ki67 or p53 expression was also significantly unfavorable.

Conclusions:
- PBK/TOPK expression is positively correlated with Ki67 and p53 expression, and can be used as an independent prognostic factor in NSCLC.


Background:
- The behavior and prognostic features of salivary gland–type neoplasms are not clearly defined because of their low incidence.

Purpose:
- To retrospectively analyze the clinicopathologic profiles of these tumors in a large series.

Methods:
- 88 patients
  - 69 mucoepidermoid carcinoma (MEC)
  - 12 adenoid cystic carcinoma (ACC)
  - 7 epithelial–myoepithelial carcinoma (EMC)
Results/Conclusions:

- No significant difference was found among MEC, ACC, and EMC groups regarding OS and DFS (Table 3).
- The clinical behavior of MEC can be predicted by pathological grade.

| Table 3. Histological Subtypes of Survival in Surgical Patients |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                         | Overall Survival (%)     | Disease-Free Survival (%) |                         |                          |                          |
| Subtype                 | 3-Year | 5-Year | 10-Year | 3-Year | 5-Year | 10-Year | 3-Year | 5-Year | 10-Year | 3-Year | 5-Year | 10-Year |
| MEC (n = 66)            | 93.1   | 89.5   | 82.6    | 0.781  | 94.7   | 87.3    | 53.7    | 0.082 |
| ACC (n = 11)            | 88.9   | 88.9   | —       | —      | 69.3   | 46.2    | —       | —     |
| EMC (n = 7)             | 100    | 100    | —       | —      | 85.7   | 85.7    | —       | —     |

Background:
- Vascular invasion (VI) has been accepted as a universally important prognostic factor for patients with lung carcinoma.
- However, the clinical significance of VI in each of the histological subtypes has been unclear.

Purpose:
- The aim of the present study was to investigate differences in the clinicopathological implications of VI between adenocarcinoma and squamous cell carcinoma.

Methods:
- 336 patients were evaluated
  - 81 cases of peripheral-type squamous cell carcinoma
  - 255 cases of adenocarcinoma

Results:
- Among the 336 patients, the five-year survival rates for those who were VI-positive and VI-negative were 38.4% and 76.3%, respectively, the difference being significant.
- Multivariate analysis identified VI as an independent prognostic factor.
- The difference in cancer-free survival between VI-positive and -negative patients was statistically significant for adenocarcinoma
- It was not significant for squamous cell carcinoma.

Conclusion:
- The authors conclude that VI is a useful prognostic indicator in lung carcinoma, although the clinical implications of VI differ between adenocarcinoma and squamous cell carcinoma.

Original Articles: Non-Neoplastic

Shino MY, et al. CXCR3 ligands are associated with the continuum of diffuse alveolar damage to chronic lung allograft dysfunction. Am J Respir Crit Care Med 2013; 188: 1117–1125.

Background:
- After lung transplantation, insults to the allograft generally result in one of four histopathologic patterns of injury:
  - (1) Acute rejection
  - (2) Lymphocytic bronchiolitis
  - (3) organizing pneumonia
  - (4) diffuse alveolar damage (DAD)
- The authors hypothesized that DAD, the most severe form of acute lung injury, would lead to the highest risk of chronic lung allograft dysfunction (CLAD) and that a type I immune response would mediate this process.
**Purpose:**
- To determine whether DAD is associated with CLAD and explore the potential role of CXCR3/ligand biology.

**Methods:**
- Transbronchial biopsies from all lung transplant recipients were reviewed.
- The association between the four injury patterns and subsequent outcomes were evaluated using proportional hazards models with time-dependent covariates.
- BAL concentrations of the CXCR3 ligands (CXCL9/MIG, CXCL10/IP10, and CXCL11/ITAC) were compared between allograft injury patterns and “healthy” biopsies using linear mixed-effects models.
- The effect of these chemokine alterations on CLAD risk was assessed using Cox models with serial BAL measurements as time-dependent covariates.

**Results:**
- There were 1,585 biopsies from 441 recipients with 62 episodes of DAD. An episode of DAD was associated with increased risk of CLAD and death.
- There were marked elevations in BAL CXCR3 ligand concentrations during DAD.
- Furthermore, prolonged elevation of these chemokines in serial BAL fluid measurements predicted the development of CLAD.

**Conclusions:**
- DAD is associated with marked increases in the risk of CLAD and death after lung transplantation.
- This association may be mediated in part by an aberrant type I immune response involving CXCR3/ligands.

**Editorial**


**Case Reports**


- The authors present a case of a patient who developed acute respiratory failure 7 days after orthotopic heart transplantation and who had been on both mycophenolate mofetil (MMF) and tacrolimus agents.
- Lung biopsy revealed features of pulmonary hemorrhage with capillaritis.
• Considered as a possible etiology, MMF was withdrawn.
• There was immediate improvement of the patient’s symptoms.
• The temporal relationship between MMF exposure and onset of pulmonary symptoms in the absence of other possible etiologies strongly suggests a causal relationship.
• Previously published reports of pulmonary toxicity from MMF included interstitial fibrosis.
• This is the first reported case of pulmonary hemorrhage with capillaritis because of administration of MMF.


• Diagnosis: Tracheal glomus tumor.