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Articles for Notation

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4. Park S, Olsen S, Ku BM, et. al. High concordance of actionable genomic
alterations identified between circulating tumor DNA-based and tissue-based
next-generation sequencing testing in advanced non-small cell lung cancer:
The Korean Lung Liquid Versus Invasive Biopsy Program. Cancer. 2021 Aug
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5. Sato T, Shimada Y, Mimae T, et. al. The impact of pathological lymph node
metastasis with lymphatic invasion on the survival of patients with clinically

Contributes to Disease Progression in Lymphangioleiomyomatosis. Am J

7. Liang RB, Li P, Li BT, et. al. Modification of Pathologic T Classification for
Non-small Cell Lung Cancer With Visceral Pleural Invasion: Data From 1,055

infiltration is associated with a higher rate of tumor spread through air spaces

Non-Neoplastic
1. Tsoyi K, Liang X, De Rossi G, et. al. CD148 Deficiency in Fibroblasts
Promotes the Development of Pulmonary Fibrosis. Am J Respir Crit Care
Med. 2021 Aug 1;204(3):312-325.

2. Gillmore JD, Gane E, Taubel J, et. al. CRISPR-Cas9 In Vivo Gene Editing for

3. Chilosi M, Poletti V, Ravaglia C, et. al. The pathogenic role of epithelial and
endothelial cells in early-phase COVID-19 pneumonia: victims and partners

Mount Sinai COVID-19 autopsy experience. Mod Pathol. 2021
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Reviews


**Letters & Case Reports**


ARTICLES FOR DISCUSSION


**Purpose:**
To investigate relationships between clinical, diagnostic, and genetic data, hypothesizing that different subgroups of PCD patients with particular clinical and diagnostic phenotypes could be identified based on underlying genotype.

**Methods:**
- Clinical and diagnostic data were retrospectively collected from PCD patients with pathogenic mutations in a PCD-associated gene.
- Phenotype data included: BMI, FEV₁, FVC, neonatal respiratory distress, wet cough, rhinitis, glue ear, cardiac situs, congenital heart disease, nasal nitric oxide, ciliary beat pattern (hs-video microscopy), TEM.
- Phenotype data was uploaded to a Symphony AyasdiAI cloud-based platform to develop a topological model. This uses a locally-linear embedding technique (which is a non-linear dimensionality reduction technique that takes complex data and summarizes it into smaller representations of their variability).
- Best defined clusters that are generated are more closely examined (using phenotype as the input and genotype as the outcome).
- Gene groups and individual genes were mapped onto the clusters to help in hypothesis generation. These were subsequently tested with stats (ANOVA)

**Results:**
- Cohort included 396 patients, 31 PCD genes.
- TEM and ciliary beat pattern mapped very closely to the corresponding gene groups.
Patients with radial spoke, central complex, or nexin-dynein regulatory complex defects had worse FEV₁ than patients with dynein gene mutations.

Patients with variants in DNAH5 (the most common genetic cause of PCD) were phenotypically diverse without a clear cluster cohort observed.

Patients with central complex and N-DRC without situs issues had increased likelihood of glue ear.

**Take home points:**

- PCD is phenotypically and genotypically diverse and this is the first study to use this new methodology for visualization and hypothesis generation to explore phenotype-genotype associations.
- The technology is promising in that several hitherto unknown associations were uncovered.
- These may form the basis for better diagnostics and a better understanding of biology of these conditions.
- The statistical power was a bit weak (owing to low numbers in a rare condition) which limited full exploration of a variety of potential associations.
- Because of the retrospective nature, recall bias may also come into play with not all parameters being equally recalled by the study participants (many occurred in neonatal life, afterall).

*Purpose:*
The authors present three cases of an unusual tumor lung condition, thus expanding the differential for giant-cell containing lesions in the lung.

*Methods:*
- Three cases were collated from the MD Anderson archives and the personal files of the author.
- All clinical information was reviewed
- IHC was performed using antibodies directed against: AE1/AE3, CK7, TTF-1, Ki-67, p40, S-100, CD68, cathepsin K, and SABT-2
- Clinical follow-up was obtained from the referring physician and medical records

*Results:*
- All 3 cases were middle-aged men (43-54 years)
- Presentations included shortness of breath, cough, chest pain
- No history of soft tissue or bone neoplasm
- All were parenchymal lung masses (2 in upper lobes, 1 in lower lobes)
- All underwent lobectomy
- Small, well-defined lesions (up to 2.4 cm)
- Histologically, low power distinct proliferation of multinucleated giant cells admixed with mononuclear cells and hemorrhage
• Mitotic figures present but modest (2-5/10 hpf)
• Positive for CD68, cathepsin K; Negative for all others. Ki-67 scattered positive
• Follow-up on only 2 patients; one well at 12 months, 1 well at 2 months

Take home points:
• These lesions appear to be distinctive from carcinoma with giant cells and sarcomas with giant cells.
• Similar to soft tissue giant cell tumors (histologically and immunohistochemically).
• Appear to be somewhat indolent (no mets, and no early evidence of adverse outcome).
• Primary differential with osteoclast-rich GC carcinoma of lung and metastatic GC tumor bone or soft tissue.

Purpose:
- Investigate the reliability of the three methods (IHC, ISH, and RNA/DNA seq) to correctly assess the ALK status of pretested NSCLE samples

Methods:
- 10 cases selected for ring trial (4 ALK+ and 6 ALK-); 2 TMAs created
- All cases tested centrelly yielding concordant results for IHC, ISH and RNA/DNAseq
- Both TMAs and the tend paraffin blocks for sequencing were evaluated by 7 experts as part of pre-test (internal ring trial)
- All cases classified as positive, negative, not evaluable (tissue not representative), or not evaluable (technical issues).
- Cases graded on a point system: a correct result rewarded with 2 points; incorrect, no points; not evaluable was given one point (but only for 1 of the cases). Maximum score was thus 20.
- Statistical analysis was done with Fleiss’ kappa values.

Results:
- 57 institutions registered for ring trial (56 from Germany, 1 from Switzerland)
- 86 registrants: 38 for IHC, 29 for ISH, 19 for RNA/DNA seq
- Only 27% used NGS routinely for clinical diagnosis.
- 87% of IHC institutions passed the ring trial; 77% reaching full score.
- Sensitivity of IHC was 92%; specificity was 100%; Kappa of .888 (almost perfect); D5F3 was most common clone, followed by 1A4 and ALK1
- 97% of ISH institutions passed the ring trial
- Sensitivity of ISH, 94%; specificity, 100%; Kappa of .896 (almost perfect)
- 95% of DNA/RNA seq institutions passed the ring trial
- Sensitivity of seq was 98.6%; specificity was 100%; Kappa was .975 (almost perfect)

Take home points:
- FISH is still regarded as the most widely deployed gold standard for ALK detection
- IHC is excellent, with most errors being interpretive rather than technical
- Only one example of false negative on DNA/RNA seq (probably due to low RNA input.
- DNA/RNA seq may be slightly superior in terms of specificity and interrater reliability, but is limited by cost, tissue quality and technical expertise.

**Purpose:**
To elucidate the long-term prognosis of AIS and MIA after complete resection.

**Methods:**
- 3170 patients with lung adenocarcinoma were retrospectively collected and re-examined according to the WHO 4th edition. AIS defined as ≤3 cm, pure lepidic growth, and no vascular or pleural invasion. MIA was defined as ≤3 cm solitary with predominantly lepidic component less than or equal to 5 mm of invasion in greatest dimension.
- 524 cases in final study cohort (207 AIS; 317 MIA)
- All clinical information extracted from medical record (age at surgery, sex, smoking status, tumor location, procedural details, margin distance).
- EGFR mutations (exon 19 del and L858R) were examined for, where available.
- Tumor recurrence was evaluated for including signs of recurrence and imaging features.

**Results:**
- 65% were women and 64% had no smoking habit.
- Lobectomy (56%), segmentectomy (18%) and wedge (26%)
- All tumors were non-mucinous
- 5% developed second primary lung cancers (new pulmonary nodules away from prior site) All that were available (96%), were histologically distinct.
- Patients with MIA were older than those with AIS (64 vs 62 years); tumor size was larger in MIA than AIS (16 vs 14 mm)
- Patients with MIA were more likely to undergo lobectomy than sublobar resection.
- No difference in distance from margin in those that underwent sublobar resections (MIA vs. AIS)
- EGFR was more common in MIA than AIS (p=0.002)
**Take home points:**
- Estimated 10-year survival rates were 100% for both MIA and AIS.
- Overall survival rates were 95.3% for AIS and 97.8% for MIA.
- Findings support distinguishing these two entities from other types of adenocarcinoma.
Neoplastic


Purpose:
To assess the yields of the hybridization-based DNA + RNA parallel sequencing assay for ALK fusion transcripts detection in comparison with IHC and RT-PCR in formalin-fixed paraffin-embedded (FFPE) specimens from a cohort of ALK-positive NSCLCs.

Take home points:
- DNA + RNA parallel sequencing assay appears to be a promising rescue technique in equivocal IHC/RT-PCR cases.
- This technique allows for seemingly reliable detection of non-EML4 ALK fusion transcripts that are consequently ALK(+).
- NGS-based RNA-seq is able to identify known fusion partners and novel or unusual partners.


Purpose:
To detect the expression of GATA3 and mesothelial markers in sarcomatoid mesothelioma, sarcomatoid lung carcinoma, and organizing pleuritis to define the reference values for various antibodies and their combinations for the differential diagnosis of the 3 entities.

Take home points:
- WT-1 has the highest individual specificity in separating sarcomatoid meso from sarcomatoid carcinoma (100%), followed by calretinin (92%) and GATA3 (83%).
- Combination of any 2 markers (WT-1, GATA3, calretinin) results in 100% specificity for sarcomatoid mesothelioma.
- The sensitivity of detected sarcomatoid mesothelioma was only 24% with WT-1/calretinin staining, but improved to 65% with addition of GATA3.
- GATA3 appears to reliably distinguish sarcomatoid mesothelioma from sarcomatoid carcinoma and pleuritis.

*Purpose:*  
To evaluate whether germline pathogenic variants in various genes are associated with earlier-onset lung adenocarcinoma.

*Take home points:*  
- Germline pathogenic variants in TP53, EGFR, BRCA2 and possibly other FA genes may be associated with earlier onset lung adenocarcinoma.  
- The current data suggest that consideration should be given to including genetic testing in screening criteria to identify carriers of high-risk pathogenic variants.  
- The results may also influence precision therapy and improve survival in these patients.


*Purpose:*  
To evaluate the additive value of the ctDNA-based NGS test when used along with the tissue-based NGS test and to evaluate the clinical utility of the ctDNA-based NGS test in comparison with SOC genotyping in advanced NSCLC.

*Take home points:*  
- ctDNA-based test identifies additional patients with actionable genomic alterations and could, therefore, be used to complement traditional tissue-based testing for NSCLC.  
- Nearly half of patients with failed tissue based NGS testing were found to have NCCN-recommended alterations that would otherwise have been undetermined (without obtaining additional tissue).


*Purpose:*
To evaluate whether pN and Ly statuses were associated with outcomes among patients who underwent surgical resection for clinically N0 NSCLC.

Take home points:
- pN and Ly statuses are independent prognostic factors in patients with clinically N0 stage I-III NSCLC.
- Patients presenting with pN+ or Ly+ disease were associated with increased rates of recurrence (lymph node or distal metastasis).
- Preoperative evaluations using high-resolution CT and PET/CT may be useful for predicting pN+ Ly+, which may help guide the selection of surgical strategy and intensive adjuvant chemotherapy.


Purpose:
To understand the mechanism of mast-cell accumulation and the role of mast cells in the pathogenesis of LAM.

Take home points:
- LAM-cells and their interactions with fibroblasts appear to attract mast cells (as determined by tryptase staining); which release tryptase and may lead to fibrosis and disease progression.
- Using a tryptase inhibitors (sodium cromoglycate and APC366) may help to slow or halt disease progression.


Purpose:
To evaluate the impact of visceral pleural invasion on survival in a large cohort of patients with NSCLC whose tumor sizes were ≤3 cm.

Take home points:
- Extent of VPI was evaluated in 1055 patients (using elastic stains, retrospectively).
- Overall survival and disease free survival are worse in patients with PL2 than those with PL0 or PL1.
- Both DFS and OS of PL0 and PL1 were, however, comparable.
- PL2 appears to be an independent adverse prognostic factor.
- PL1 should remain defined as T1 (not T2).

**Purpose:**
To investigate whether immune cell infiltration is associated with the occurrence of STAS and clinical outcome of the disease.

**Take home points:**
- High density of CD68(+) tumor associated macrophages (TAM) was independently predictive of STAS
- High density of CD68(+) TAM was also predictive of recurrence on univariate analysis.
- STAS, in this study, was also correlated with aggressive tumor behavior.

**Non-neoplastic**


**Purpose:**
To delineate the mechanism(s) by which CD148 regulates fibroblast activation and its role as a therapeutic target in IPF.

**Take home points:**
- Fibroblast CD148 expression is downregulated in IPF lungs
- Silencing CD148 increases extracellular matrix production and resistance to apoptosis
- CD148 activation reduces p62 accumulation which inhibits NF-κB–mediated profibrotic gene expression
- Targeting the CD148 phosphatase with activating ligands such as SDC2-pep may represent a potential therapeutic strategy in IP


**Purpose:**
To report interim data from an ongoing clinical study evaluating single ascending doses of NTLA-2001 for TTR editing and knockout in the treatment of patients with hereditary ATTR amyloidosis with polyneuropathy.
Pre-clinical studies showed durable knockout of TTR after a single dose
Few adverse events reported in month 1
Dose-dependent pharmacodynamic effects were noted
In a small group of patients (6), administration of NTLA-2001 was associated with reduction in TTR serum concentration mediated by knockout of TTR.


Purpose:
To report findings from 100 consecutive autopsies of patients dying of COVID-19, summarizing the key histopathologic findings within each organ system. The findings are presented in the context of relevant literature reviews.

Take home points:
• DAD seen in 83% (2/3 acute; 1/3 organizing)
• Septal capillary proliferation seen in 19%
• Pulmonary thromboemboli seen in 6%
• Median time between symptom onset and death was 11 days for acute DAD; 26 days for organizing DAD.
• Pneumocyte hyperplasia seen in all cases of DAD, some with bland cells, others with pleomorphic cells.
• Systemic effects include hypercoagulability, hyperinflammation, and endothelial dysfunction.

REVIEWS


Summary:
The article reviews the role of epithelial and endothelial cells in early COVID-19 pneumonia. The observations of DAD and pneumonia do not adequately explain the vascular changes (vessel enlargement) noted on CT in these patients, nor does it explain the preservation of lung compliance. These may, in part, be explained by peculiar morphological and morpho-phenotypical changes including hyper-expression of phosphorylated STAT3 and immune...
checkpoint molecules (PD-L1 and IDO) in alveolar-epithelial and endothelial cells.


Summary:
The authors review the role of immune checkpoint inhibition in patients with EGFR-mutated NSCLC.


Summary:
This review sets out to put into context our current understanding of the lung microbiome in the post-lung transplant patients. They explore the interactions between the microbiome and the host and the role of the microbiome in complications that arise in the post-transplant setting. They conclude by laying out their perspective on the critical outstanding research questions in this arena.


Summary:
This review summarizes the biology of NRG1 fusions as well as their clinical detection. They note that these fusions tend to drive adenocarcinoma over other morphologic sub-types of lung cancer, but also explain the fusion partners may result in differing histologies. The conclude by reviewing treatment implications and a brief discussion on future direction(s).


Summary:
The authors aim to provide a pragmatic update on the use of pan-TRK IHC. Selected examples of the different IHC staining patterns across multiple histologies are presented on data gathered from PubMed-resulted literature reviews. The review covers a wide variety of malignancies, including lung
adenocarcinoma. NTRK fusions occur in fewer than 1% of NSCLC and are usually adenocarcinomas.

**CASE REPORTS / LETTERS TO THE EDITOR / EDITORIALS**


   **Summary:**
   This article represents an editorial to the Tsoyi et al. work on CD148-driven fibroblast activation in IPF/UIP. The author is very positive with the work overall and believes it to be an important step in the further understanding of not only the biology but also therapeutic development for IPF.


   **Summary:**
   Simple case presentation of a young boy with a history of asthma who experienced rapid development of plastic bronchitis. The images (both gross and microscopic) in this case report are, incidentally, beautiful.


   **Summary:**
   The authors present a case of AL amyloidosis with diffuse interstitial infiltration that presents with emphysema. They hypothesize that the unusually severe disease in the lower lobe may be exacerbated by the interstitial amyloid deposition.


   **Summary:**
   This is the accompanying editorial to the article that was one of our subjects of discussion this month. The author commends Shoemark et al. for their work in this field, acknowledging the limitation we noted during the discussion. They also put emphasis on the need for large collaborative
research networks as a way of overcoming the rarity of this condition (particularly in light of the genetic and phenotypical heterogeneity).


Summary:
This is an editorial on the Babaei-Jadidi et al. paper on mast cells in LAM. The author is very laudatory about the significance of the paper and how it moves us forward on the understanding of LAM biology/therapy. She closes by indicating the future studies will be necessary to further explore the synergistic roles of cromoglycate and sirolimus in patients.


Summary:
The authors present a case report of a metastatic mucinous adenocarcinoma harboring both KRAS and GNAS mutations arising within a type 1 CPAM. They also do a literature survey of the topic, showing that the occurrence is uncommon and the behavior, somewhat indolent.