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Articles for Discussion

Jin et al. Frequent aerogenous spread with decreased E-cadherin expression of ROS1-rearranged lung cancer predicts poor disease-free survival. Lung Cancer. 2015 Sep;89(3):343-9


Wells et al. Evaluating the utility of trefoil factor 1 as a mammary-specific immunostain compared and in conjunction with GATA-3 and mammaglobin in the distinction between carcinoma of breast and lung. Am J Clin Pathol. 2015 Sep;144(3):444-51.


Background:
- ROS1-rearranged non-small cell lung carcinoma (NSCLC) share similarities with ALK-rearranged NSCLC including young age of onset, non/light smoking hx, “solid signet-ring cell” and “mucinous cribriform” morphology, and sensitivity to most ALK inhibitors.
- ALK-rearranged tumors reported to have decreased E-cadherin expression, but no reports on ROS-1 rearranged tumors.

Purpose:
- Evaluate E-cadherin expression in ROS1-rearranged NSCLC
- Correlate with clinicopathologic features

Methods:
- ROS1-rearrangement assayed by both FISH and IHC; E-cad IHC
- Histologic analysis:
  - Adenocarcinomas (Adca) classified by WHO 2015 criteria
  - Tumor size, p stage, predominant growth pattern, aerogenous spread, invasion status (pleura, lymphatic, vascular)
- Additional mutational analysis for EGFR (exons 18-21), KRAS (codons 12, 13, 61) using PCR and direct DNA sequencing or pyrosequencing, and break-apart FISH for ALK rearrangement

Results:
- 469 Adca (62.2%), 254 Squamous cell (33.7%), 31 (4.1%) other NSCLC
- 549 patients stage I and II (72.8%)
- 10 tumors w/ ROS1 rearrangements
  - All Adca (1 being sarcomatoid)
  - 1.3% overall, 1.9% of Adca
  - 7 non-smokers, 3 smokers (of which 1 current)

Patient and molecular features:
- Younger women overrepresented (age: p=.042, sex: p=.014)
- Mutually exclusive with EGFR and ALK, single case of KRAS co-mutation
Pathologic features:
- Micropapillary pattern more common in ROS1-rearranged (8 of 10) than ROS1 wild type ($p<.001$)
- Aerogenous spread more common in ROS1-rearranged (all 10), than ROS1 wt ($p=.002$)
- Predominant pattern of the 9 Adcas: 3 solid, 3 acinar, 2 micropapillary, 1 lepidic
- “Solid, signet ring” focally in 3 cases, “cribriform” focally in 9 cases

ROS1 and E-cadherin expression:
- Decreased E-cad more common in ROS1-rearranged (all 10) than ROS1 wt tumors ($p=.049$)
- Decreased E-cad also more common than in EGFR mutant, KRAS mutant, and EGFR/KRAS/ALK/ROS-1 negative tumors
- However, similar E-cad expression compared to ALK-rearranged tumors

**ROS1 FISH versus IHC:**
- Best combination of sensitivity (90.0%) and specificity (93.5%) achieved with an "H-score" ≥ 100
- By comparison, using extent ≥75%, sens=90.0%, spec=91.8%
- By comparison, using intensity ≥3+, sens=60.0%, spec=99.6%

**Outcomes:**

![Graph A](image1.png)
![Graph B](image2.png)

- Shorter DFS (27 months vs 55 months), but not overall survival
- However, ROS1 was NOT an independent prognostic factor on multivariate analysis

**Discussion points:**
ROS1-rearranged tumors more likely to
- Show micropapillary growth and aerogenous spread than ROS1-wt tumors
- Decreased E-cad expression
- Decreased DFS, but not OS
- Speculation: Perhaps this is mediated by decreased E-cad expression (a marker of epithelial-mesenchymal transition). Other data (not provided) of EMT markers (IHC for vimentin, snail, b-catenin, and matrix metalloproteinase) were not significantly different in ROS1 vs ROS-wt tumors
- Authors recommend ROS1 IHC for clinical use

Background:
- Although TNM stage represents the most reliable prognostic predictor in NSCLC, important advances have been made in histologic subtyping and genetic characterization of lung adenocarcinoma, w/ corresponding improvement in prognostic groups and disease control via tailored drug therapies
- Squamous cell lung cancer (SQLC) may see similar advances since The Cancer Genome Atlas Research Project published a comprehensive genomic and epigenomic characterization in 2012, with potential druggable genes/pathways

Purpose:
- Create prognostic nomogram based on validated and putative clinicopathologic biomarkers for resected SQLC (R-SQLC)

Methods:
- R-SQLC with stored tissue available for biomolecular analysis with at least 2 years follow up, who underwent surgery since 2009 in five Italian hospitals
- Develop and validate a risk-class model to identify the best and worst performers based on (very complex!) multivariate analysis exploring the independent impact of clinicopathologic factors on OS, cancer-specific survival (CSS, time between diagnosis and death due to cancer progression), and DFS.

Results:
- 494 evaluable patients
- 403 (81.6%) males
- Histologic grade: 44.3% grade 1-2, 35.9% grade 3, 19.8% grade unknown
- Independent predictors of DFS and OS on multivariate analysis (MVA) –
  - Age ≤ 68y
  - T-descriptor
  - Negative nodes
  - Grades 1-2
- Independent predictors of CSS on MVA –
  - T-descriptor
  - Negative nodes
Based on hazard ratios on MAV, developed Prognostic Score as follows:

<table>
<thead>
<tr>
<th>Disease-Free Survival</th>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>≤68</td>
</tr>
<tr>
<td>T-descriptor according to TNM 7th edition</td>
<td>1–2</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Negative</td>
</tr>
<tr>
<td>Grading</td>
<td>1–2</td>
</tr>
</tbody>
</table>

TNM, tumor, node, metastasis.

Using a two-class model, a statistically significant prognostic difference between patients at low (score ≤2) and high (score >2) risk was determined for all outcomes (DFS, OS, CSS) at p<0.0001

Using a three-class model, statistically significant prognostic groups could also be determined: (a) low (score 0-2), (b) intermediate (3-4), and (c) high (5-6). Data for CSS shown below:

Discussion points:
- Not sure this is a significant advance: TNM is corroborated (yet again, as if we didn’t already know that) as important, along with a clinical factor (age)
- Authors acknowledge that histologic grading/subtyping has NOT been shown to be independent prognostic predictor in other studies, and mostly side-step the issue of reproducibility
• Also acknowledge that none of the parameters are novel, only the particular combination and the weight they assign them in their risk-models.


Background:
• 3-4% of breast cancer (BC) patients have a solitary pulmonary nodule on imaging studies, of which 43-83% represent metastatic BC
• However, primary lung cancer (PLC) is the 2nd most common malignancy among US women, behind only BC
• Chest irradiation confers a 3-fold increased risk of PLC in ipsilateral breast
• Sensitivity and specificity of ER, PR, and mammaglobin for BC and TTF-1 and napsin A for PLC are less than 100%.
• Trefoil factor 1 (TFF1) is a protein expressed in mucins in the GI tract (mostly stomach) and in the epithelium of the breast and in BC

Purpose:
• Investigate the utility of an IHC panel comprising mammaglobin, GATA-3, and TFF1, focusing on metastatic triple negative BC (TNBC) vs PLC

Methods:
• TMA of 365 BC
  o 245 IDC, of which 142 TNBC
  o 120 metastatic BC at distant sites
• TMA of 338 PLC
  o 271 Adca, 45 squamous, 8 adenosquamous
• IHC staining to obtain H-score (HS: sum of staining intensities x % of cells at each intensity)
• An optimum HS cutoff point for positivity established for each antibody at which the BC and PLC dichotomized with the highest odds ratio
  o Used positivity cutoff of HS>5 for GATA-3 and TTF1 (6% of cells at weak intensity, 3% at moderate, and 2% at strong intensity)
  o Used positivity cutoff HS>0 for mammaglobin (any appreciable staining in any cell)

Results:
Overall (among all breast tumors):
GATA-3: highest sensitivity and intermediate-high specificity (+ in 10% of PLC)
Mammaglobin: lowest sensitivity but highest specificity
TFF1: relatively low sensitivity and specificity

Sensitivity of markers decreases with TNBCs; Specificity tends to hold steady when the lung cancer is moderately or poorly differentiated.

Discussion points:
- TFF1 does NOT improve on the diagnostic accuracy of GATA-3 and mammaglobin
- TFF1 expression believed to be estrogen linked
- Discriminating TNBC from poorly and mod-differentiated PLC remains a challenge
Background:
- In CVID patients, morbidity and mortality from infectious complications has decreased since the introduction of high-dose intravenous immunoglobulin or subcutaneous gammaglobulin;
- However, non-infectious complications have increased, including autoimmunity, inflammatory bowel disease, enteropathy, hepatitis, lymphoproliferative disease, and diffuse parenchymal lung disease (DPLD);
- The differential diagnosis of DPLD in CVID patients is broad and includes infection, hypersensitivity pneumonia, cryptogenic organizing pneumonia, lymphoma, and “GL-ILD” - the latter being the most common cause.
- Acknowledge some overlap between GL-ILD and LIP and FB.

Purpose:
- Systematic characterization of histopathologic and immunohistochemical features of GL-ILD.

Methods:
- 16 patients with CVID (females=10, age range 19-57y, mean 37y) and GL-ILD who underwent surgical lung bx (VATS or open)
- Histologic features: +/- FB, LIP, epithelioid granulomata, organizing pneumonia, interstitial fibrosis, alveolar remodeling (honeycomb change). GMS and AFB on all
- IHC for lymphoid markers: CD3, CD4, CD8, CD19, CD20, CD138, PAX5, and Fox-P3, quantified by ACIS

Results:
- “Nodular peribronchiolar inflammation” in all (mild in 25%, moderate in 56%, severe in 19%)
- “Dense, nodular, and diffuse” interstitial chronic inflammation in all (mild in 19%, moderate in 25%, severe in 56%)
- Both components “marked” in 10 (62.5%) of 16
In 1 case, there was paucity of inflammation and, by contrast, “rather advanced interstitial fibrosis with evidence of remodeling”

Non-necrotizing granulomata (NNG) in 15 (93.75%) w/in interstitium, bronchovascular bundles, and (occasionally) alveolar spaces; GMS and AFB negative

Organizing pneumonia in 14 (87.5%)

Interstitial fibrosis in 12 (75%):
  - Mild in 5 (31.25%)
  - Moderate in 4 (25%)
  - Severe in 3 (18.75%)

Immunohistochemistry:
  - CD3/CD+ T cells predominated in all but 2 cases where CD20+ B cells predominated
  - B cells present in all cases except 1
  - In areas of FB, T cells predominated over B cells (really?)
  - There were NO regulatory T cells (based on Fox P3)
  - Cases with alveolar remodeling demonstrated strong CD138 within epithelium
Take-home points (per authors):

- GL-ILD a conglomerate of findings including usually and most prominently peribronchiolar and interstitial lymphoid inflammation with NNG
- Recommend staining for lymphoid subsets due to (alleged) treatment implications targeting B-cells (rituximab) and T cells (azathioprine).
- Low numbers of regulatory T cells (in peripheral blood in CVID patients) correlates with autoimmunity and granulomatous disease, and therefore this may contribute to pathogenesis of lung disease in these patients
- Suggest that interstitial fibrosis may be a marker of disease progression
- GL-ILD can be seen in other primary immunodeficiencies (hypogammaglobulinemia)

Questions:

- Are GL-ILD and FB/LIP distinct entities?
- Is fibrosis an important component?

**Articles for Notation**

*Neoplastic*


Koh et al. Clinicopathologic analysis of programmed cell death-1 and programmed cell death-ligand 1 and 2 expressions in pulmonary adenocarcinoma: comparison with histology and driver oncogenic alteration status. Mod Pathol. 2015 Sep;28(9):1154-66


Kadota et al. Tumoral CD10 expression correlates with high-grade histology and increases risk of recurrence in patients with stage I lung adenocarcinoma. Lung Cancer. 2015 Sep;89(3):329-36.

Kadota et al. Tumor Budding Correlates With the Protumor Immune Microenvironment and Is an Independent Prognostic Factor for Recurrence of Stage I Lung Adenocarcinoma. Chest. 2015 Sep;148(3):711-21


Specht et al. Comparison of immunoreactive score, HER2/neu score and H score for the immunohistochemical evaluation of somatostatin receptors in bronchopulmonary neuroendocrine neoplasms. Histopathology. 2015 Sep;67(3):368-77.


Zhang et al. Testicular orphan receptor 4 (TR4) is a marker for metastasis and poor prognosis in non-small cell lung cancer that drives the EMT phenotype. Lung Cancer. 2015 Sep;89(3):320-8.

Case Reports / Letters to the Editor


Non-neoplastic

Xu et al. MicroRNA-144 dysregulates the transforming growth factor-β signaling cascade and contributes to the development of bronchiolitis obliterans syndrome after human lung transplantation. J Heart Lung Transplant. 2015 Sep;34(9):1154-62


Akgun et al. SilicosisAppears Inevitable Among Former Denim Sandblasters: A 4-Year Follow-up Study. Chest. 2015 Sep;148(3):647-54

Case Reports / Letters to the Editor