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Articles for Discussion


AIM:
- To elucidate the clinical, radiologic, and histologic features of LD-CTD

METHODS:
- The authors retrospectively reviewed 44 consecutive patients with LD-CTD who underwent surgical lung biopsy
- Patients were identified as having LD-CTD if
  - they had specific autoantibodies but
  - did not meet the criteria for connective tissue disease
- The authors assessed
  - The major histologic patterns according to the 2013 classification of idiopathic interstitial pneumonias (IIPs)
  - Histologic features characteristic of LD-CTD (see Fig. 1 below), including
    - lymphoid aggregates with germinal centers
    - extensive pleuritis
    - prominent plasmacytic infiltration
    - and dense perivascular collagen
  - High-resolution CT (HRCT) scan patterns, and
  - Prognosis
RESULTS:

**TABLE 1** Major Histologic Pattern From the SLB Specimens in 44 Patients With LD-CTD

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Subjects, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>25 (57)</td>
</tr>
<tr>
<td>NSIP</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (14)</td>
</tr>
<tr>
<td>OP</td>
<td>1</td>
</tr>
<tr>
<td>DAD</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Airway-centered interstitial fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Mixed pattern(^a)</td>
<td>2</td>
</tr>
</tbody>
</table>

**TABLE 2** Characteristic Histologic Features of LD-CTD

<table>
<thead>
<tr>
<th>Histologic Features</th>
<th>Total (N = 44)</th>
<th>Histologic UIP (n = 25)</th>
<th>Histologic NSIP (n = 13)</th>
<th>Histologic Other (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid aggregates with germinal centers</td>
<td>21 (48)</td>
<td>12 (48)</td>
<td>8 (62)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Extensive pleuritis</td>
<td>19 (43)</td>
<td>11 (44)</td>
<td>5 (38)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Prominent plasmacytic infiltration</td>
<td>32 (73)</td>
<td>18 (72)</td>
<td>11 (85)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Dense perivascular collagen</td>
<td>20 (45)</td>
<td>11 (44)</td>
<td>6 (46)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Two or more histologic features of LD-CTD</td>
<td>30 (68)</td>
<td>15 (60)</td>
<td>11 (85)</td>
<td>4 (67)</td>
</tr>
</tbody>
</table>

**TABLE 4** Radiologic Probability of UIP Pattern Segregated by Histologic Pattern

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>Total</th>
<th>HRCT Scan Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>UIP Pattern</td>
</tr>
<tr>
<td>Histologic UIP</td>
<td>25</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Histologic NSIP</td>
<td>13</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Histologic other</td>
<td>6</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

- After multidisciplinary discussion (MDD)
  - 25 patients with an h-UIP were labeled as having unclassifiable IIP (n=18) or IPF (n=7)
In contrast, survival was not associated with HRCT scan pattern (P = .79).

CONCLUSIONS:
- The major histologic patterns in LD-CTD were UIP followed by NSIP.
- Two-thirds of patients had characteristic histologic features for LD-CTD.
- A majority of patients with h-UIP were considered to have unclassifiable IIP based on MDD.
- Patients with h-UIP had worse survival than those with h-NSIP.

BACKGROUND:
- The programmed death ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) pathway is one of the most important checkpoint pathways for mediating tumor-induced immune suppression through T-cell exhaustion
- PD-L1 binds to B7.1 and PD-1 on cytotoxic T cells, disabling the anticancer immune response
- Recently, targeted therapies using monoclonal antibodies against components of this pathway have been shown to reduce tumor burden in patients with non-small cell lung cancer (NSCLC)
- However, the prognostic significance of PD-L1 expression is controversial and the precise mechanisms of PD-L1 gene activation in lung cancer have yet to be clarified

AIMS
- To investigate
  - Copy number alterations (CNAs) in the PD-L1 gene
  - Possible associations between PD-L1 CNAs and lung cancer biology
  - CNAs in the Janus kinase 2 (JAK2) gene
  - The influence of JAK2 CNAs on the PD-L1/PD-1 pathway

METHODS:
- CNAs were analyzed in 94 surgically resected lung cancer samples

RESULTS:
- Patients
  - Five samples were shown to have PD-L1 gene amplification, whereas 89 samples did not
  - The patients with PD-L1 amplification had worse prognoses than did those without PD-L1 amplification
  - Genetic amplification of the PD-L1 gene was correlated with JAK2 gene amplification
- Cancer cell lines
  - The lung cancer cell line HCC4006 was found to harbor both JAK2 and PD-L1 amplification
  - Flow cytometry analyses revealed the level of PD-L1 protein expression to be higher in HCC4006 cells than in other NSCLC cell lines
  - Expression of the PD-L1 protein was significantly reduced by the JAK2 inhibitor TG-101348 and the signal transducer and activator of transcription 3 (STAT-3) inhibitor BP-1-102, but not by the STAT1 inhibitor fludarabine

CONCLUSIONS:
- There is a certain population of patients with primary NSCLC who harbor simultaneous amplification of the PDL1 and JAK2 genes and
- In these patients, PD-L1 protein expression is synergistically upregulated by PD-L1 gene amplification and JAK2/STAT signaling
BACKGROUND:
- Clinical trials of therapies for non-small cell lung cancer (NSCLC) are increasingly requiring mandatory tumor samples or research biopsies

AIM:
- To assess the impact of research biopsies on the enrollment of patients with advanced NSCLC in clinical trials

METHODS:
- The cases of patients with advanced NSCLC who had been evaluated for clinical trials of systemic therapy at the Princess Margaret Cancer Centre (Toronto, Canada) from January 2007 to March 2015 were reviewed

RESULTS:
- **Trial characteristics**
  - 38 trials required tumor samples for enrollment
  - 6 mandated repeat biopsies, whereas 32 permitted use of archival samples

**Trial treatment in trials with and without a mandatory tissue requirement**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All therapeutic trials (549 consents)</th>
<th>Tissue not required (17 trials, 102 consents)</th>
<th>Mandatory tissue (37 trials, 447 consents)</th>
<th>Repeat biopsy not required (31 trials, 360 consents)</th>
<th>Mandatory repeat biopsy (6 trials, 87 consents)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving study treatment, n (%)</td>
<td>329 (60%)</td>
<td>85 (83%)</td>
<td>244 (55%)</td>
<td>211 (59%)</td>
<td>33 (38%)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

- In 549 encounters during which participation in a therapeutic trial was offered, 60% received study treatment
- More patients received study treatment (83% versus 55%, p < 0.0001) and study treatment was started earlier (after 9 days versus after 16, p = 0.002) when the trial did not have a mandatory tissue sample requirement.

- A similar trend was noted for trials permitting use of archival tissue versus mandatory repeat biopsies.

- **Reasons for not proceeding to study treatment**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mandatory repeat biopsy (n = 54)</th>
<th>Repeat biopsy not required (n = 149)</th>
<th>Tissue not required (n = 17)</th>
<th>Total (N = 220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required biomarker not present</td>
<td>24 (45%)</td>
<td>52 (35%)</td>
<td>-</td>
<td>76 (34%)</td>
</tr>
<tr>
<td>Patient withdrew consent</td>
<td>5 (9%)</td>
<td>34 (23%)</td>
<td>4 (23%)</td>
<td>43 (20%)</td>
</tr>
<tr>
<td>Clinical deterioration or death</td>
<td>8 (15%)</td>
<td>27 (18%)</td>
<td>2 (12%)</td>
<td>37 (17%)</td>
</tr>
<tr>
<td>Other exclusion criteria</td>
<td>11 (20%)</td>
<td>13 (9%)</td>
<td>10 (59%)</td>
<td>34 (15%)</td>
</tr>
<tr>
<td>Insufficient tissue</td>
<td>5 (9%)</td>
<td>17 (11%)</td>
<td>-</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>6 (4%)</td>
<td>1 (6%)</td>
<td>8 (4%)</td>
</tr>
</tbody>
</table>

**CONCLUSION:**
- A growing number of trials of therapies for advanced NSCLC are requiring tumor tissue for treatment eligibility as patient selection becomes increasingly driven by molecular analysis of tumor tissue.

- Molecular selection was the most common cause of trial ineligibility; however, the requirement for additional tumor tissue poses a significant barrier to clinical trial enrollment, with repeat biopsies, tissue acquisition, and central biomarker testing resulting in significant delays in initiating study treatment.

- Potential solutions include:
  - routine tissue banking at diagnosis
  - facilitation of the use of available diagnostic samples for trials
  - development of peripheral blood assays for trials
  - faster central laboratory turnaround time or permission for accredited local testing, and
  - more resources for timely acquisition of tissue for clinical trials.

BACKGROUND:
- Rearrangements of RET are rare oncogenic events in patients with non-small cell lung cancer (NSCLC)
- While the characterization of Asian patients suggests a predominance of nonsmokers of young age in this genetically defined lung cancer subgroup, little is known about the characteristics of non-Asian patients

AIM:
- To analyze a European cohort of patients with RET rearranged NSCLC

METHODS:
- 997 patients with KRAS/EGFR/ALK wild-type lung adenocarcinomas were analyzed using fluorescence in situ hybridization for RET fusions
- Tumor specimens were molecularly profiled and clinicopathological characteristics of the patients were collected

RESULTS:
- Rearrangements of RET were identified in 22 patients, with a prevalence of 2.2% in the KRAS/EGFR/ALK wild-type subgroup
- Co-occurring genetic aberrations were detected in 10 patients, and the majority had mutations in TP53
- The median age at diagnosis was 62 years (range, 39-80 years; mean ± SD, 61 ± 11.7 years) with a higher proportion of men (59% versus 41%)
- There was only a slight predominance of nonsmokers (54.5%) compared to current or former smokers (45.5%)
CONCLUSIONS:

- Patients with RET rearranged adenocarcinomas represent a rare and heterogeneous NSCLC subgroup
- In some contrast to published data, the authors saw a high prevalence of current and former smokers in their white RET cohort
- The significance of co-occurring aberrations is unclear
**Articles for Notation**

**Original Article**


**AIM:**
- The aim of this study is to identify the expression of fibroblast growth factor (FGF) 1 in primary human NSCLC tissues and evaluate its clinical significance for NSCLC patients.

**METHODS:**
- Archived tissues from NSCLC (n = 113) and adjacent normal lung tissues (n = 71) were examined for the immunohistochemical expression of FGF1.
- Then we analyzed the correlations of FGF1 expression with clinicopathological factors and overall survival of the patients.

**RESULTS:**
- FGF1 expression was identified in the cytoplasm or both cytoplasm and nucleus of NSCLC cells.
- Immunoreactive scores of FGF1 were significantly higher in NSCLC specimens than in peritumoral normal tissues.
- High expression of FGF1 (immunoreactive score >3) was detected in 61.9% (70/113) of NSCLC specimens, and
- high FGF1 expression in cancer cells was significantly correlated with larger primary tumor size, squamous cell carcinoma (SQCC), and vascular invasion.
- In addition, FGF1 expression was correlated with intratumoral microvessel density in both SQCC and adenocarcinoma subgroups.
- Moreover, NSCLC patients with high FGF1 expression had a significantly lower overall survival rate, compared with those with low FGF1 expression.
- Furthermore, subgroup analyses showed that FGF1 expression was associated with poor prognosis in lung SQCC, but not in adenocarcinoma.

**CONCLUSIONS:**
- These findings suggest that the presence of FGF1 in NSCLC cells may serve as a prognostic indicator and a potential therapeutic target for NSCLC patients, especially for lung SQCC.
Review Articles


Case Reports


CASE PRESENTATION:
- Seven years after left hemicolecotomy and radical lymph nodal dissection followed by adjuvant chemotherapy for colorectal cancer (histotype, adenocarcinoma; stage, pT3N2M0; grading, G2), a slight increase in carcinoembryonic antigen levels (6.2 ng/mL; range, 0-5 ng/mL) was detected in a 79-year-old man.
- He was a heavy smoker with history of an interstitial fibrotic lung disease with associated areas of emphysema.

DIAGNOSES:
- Primary invasive lung adenocarcinoma
- Usual interstitial pneumonia pattern