# PULMONARY PATHOLOGY JOURNAL CLUB
(December 20, 2010)

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### II. ARTICLES FOR NOTATION ONLY

#### Neoplastic diseases

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I. DISCUSSION ARTICLES


Purpose:
• To report 4 cases of neuroendocrine proliferation in intrathoracic LNs (ILNs) of patients with primary lung adenocarcinoma.

Results:
• All patients had a single lung mass without mediastinal lymphadenopathy.
• Mediastinal staging was done by either mediastinoscopy or thoracotomy and none of them had metastasis from adenocarcinoma in any LN.
• One patient
  o had three ILNs positive for neuroendocrine proliferation measuring 1.7, 1.8, and 4.0 mm, respectively and a minute tumorlet less than 1.0 mm in the lung.
• Three other patients
  o had small areas of neuroendocrine proliferation no more than 1 mm in single ILN without any lung neuroendocrine lesion.
• These cells were positive for
  o synaptophysin, chromogranin, CD56, CK7 and TTF-1.

Conclusions:
• These findings suggest that neuroendocrine lesion can be incidentally identified in ILNs.
• Close clinical follow-up is warranted as metastasis from or synchronous lesions in adjacent organs cannot be excluded.
Marchevsky AM, et al. The presence of isolated tumor cells and micrometastases in the intrathoracic lymph nodes of patients with lung cancer is not associated with decreased survival. Hum Pathol 2010;41:1536–1543

Purpose:
- To investigate the prognostic role of small intrathoracic nodal metastases in primary patients with lung cancer.

Methods:
- The intrathoracic lymph nodes from 266 clinical stage I non–small cell carcinoma patients treated at Cedars Sinai Medical Center from 1992 to 2006 were evaluated with immunohistochemistry for keratin AE1/AE3 for the presence of isolated tumor cells and micrometastases, as defined by American Joint Commission on Cancer criteria, correlated with survival using the Kaplan-Meier method and analyzed with power analysis.
- The English literature from 1995 to 2008 was reviewed to identify best available evidence regarding the prognostic value of isolated tumor cells and micrometastases detected with various immunohistochemistry and molecular methods in non–small cell carcinoma patients.
- Results were combined with the authors’ own data and evaluated with metaanalysis using Comprehensive Meta-analysis 2.0 software (Biostat Inc, Englewood, NJ).

Results:
- Isolated tumor cells and micrometastases were detected in 8 and 67 of 4148 lymph nodes, respectively, and their presence was not significantly associated with survival.
- Power analysis showed that 3060 cases followed up for 60 months would be needed to achieve 80% power in a study designed to detect survival differences between patients with negative nodes and micrometastases.
- Meta-analysis of 835 non-small cell carcinoma patients reported in 13 studies showed scanty data to evaluate patients with isolated tumor cells, no significant association between micrometastases and survival and significant data heterogeneity.

Conclusions:
- Current best evidence suggests that non-small cell carcinoma patients should probably not be “upstaged” in the presence of isolated tumor cells and micrometastases.
- There is no data demonstrating survival benefits for patients treated with adjuvant chemotherapy and/or radiation therapy because of the presence of small nodal metastases.
Background:
- Increased expression of CD146, a cell adhesion molecule, has been reported to be closely associated with an advanced stage of malignant melanoma, prostate cancer, and ovarian cancer.

Purpose:
- To evaluate the utility of CD146 in discriminating between malignant pleural mesothelioma and reactive mesothelium.

Methods:
- A total of 51 cases (23 malignant pleural mesothelioma and 28 reactive mesothelium).
- Smear specimens of effusion fluids.
- Two CD146 antibody clones (OJ79 and EPR3208).
- Immunocytochemical stains were semiquantitatively scored on the basis of immunostaining intensity (0, negative; 1, weak positive; 2, moderate positive; and 3, strong positive).

Results:
- CD146 expression was detected in 15 of 16 malignant pleural mesothelioma with median immunostaining score of 3 by OJ79, and in 19 of 21 malignant pleural mesothelioma with median immunostaining score of 2 by EPR3208.
- Strong immunoreactivity of CD146 was observed at the apposing surfaces of cell–cell interactions on the plasma membrane of mesothelioma cells.
- In addition, one OJ79-negative case of malignant pleural mesothelioma was positive for CD146 by EPR3208 and two EPR3208-negative cases of malignant pleural mesothelioma were CD146 positive by OJ79, showing that all 23 malignant pleural mesothelioma cases were positive for CD146 by either OJ79 or EPR3208.
- On the other hand, CD146 expression was undetectable in all reactive mesothelium cases by OJ79 and EPR3208.
- The sensitivity of OJ79 and EPR3208 was 94 and 90%, respectively, and the specificity was 100% for both clones.

Conclusions:
- CD146 is a sensitive and specific immunocytochemical marker enabling differential diagnosis of malignant pleural mesothelioma from reactive mesothelium.
Figure 4. Distributions of CD146 immunostaining score. (a) Score of OJ79. (b) Score of EPR3208. Open circles represent immunostaining scores listed in Table 1 and the horizontal bars indicate the median value. CD146 expression detected by both clones OJ79 and EPR3208 in malignant pleural mesothelioma was significantly higher than that in reactive mesothelium \((P<0.001)\). RM, reactive mesothelium; MPM, malignant pleural mesothelioma.

Figure 3. Different expression patterns of CD146 and EMA. (a-d) Malignant pleural mesothelioma—case no. 11. (a) Papanicolaou stain. (b-d) Immunostaining with EMA, OJ79, and EPR3208, respectively. CD146 expression is detected by OJ79 and EPR3208 at the apposing surfaces of cell-cell interactions (arrows) (c, d), whereas EMA expression is mainly detected in the periphery of cell clusters (b). Scale bar indicates 50 μm.
Background:
- **Surfactant homeostasis**
  - Surfactant homeostasis is maintained by balanced production and clearance, which are tightly regulated.
  - Surfactant lipids and proteins are synthesized in type II cells and secreted into alveoli.
  - Surfactant is cleared by uptake into alveolar epithelial cells that either recycle or catabolize it or by uptake and catabolism in alveolar macrophages.
  - Clearance (but not uptake) of surfactant lipids and proteins by alveolar macrophages requires stimulation by granulocyte-macrophage colony-stimulating factor (GM-CSF).
- **GM-CSF**
  - A hematopoietic cytokine that signals via heterodimeric cell-surface receptors comprised of ligand-binding α (CD116) and affinity-enhancing β (CD131) chains.
  - Controls myeloid cell survival, proliferation, differentiation, and functional activation.
  - Required for the terminal differentiation of alveolar macrophages.
  - Regulates numerous functions of alveolar macrophages including the ability to catabolize surfactant lipids and proteins.
- **PAP**
  - A syndrome characterized by the accumulation of surfactant in alveolar macrophages and alveoli resulting in respiratory insufficiency.
  - PAP comprises a heterogeneous group of diseases.
- **Autoimmune PAP**
  - Represents approximately 90% of cases and occurs in men, women, and children with an overall prevalence of approximately 6 to 7 per million.
  - It is caused by high levels of neutralizing GM-CSF autoantibodies that block GM-CSF signaling in vivo.
- **Secondary PAP**
  - The next most common clinical form, accounting for approximately 8–9% of cases.
  - It occurs in the context of a very heterogeneous group of underlying diseases that reduce either the number or the intrinsic surfactant clearance capacity of alveolar macrophages.

Purpose:
- The authors hypothesized that an increased serum GM-CSF level may identify individuals with **PAP caused by GM-CSF receptor dysfunction**.

Methods:
- The authors screened 187 patients referred to them for measurement of GM-CSF autoantibodies to diagnose autoimmune PAP.
Results:

- Of the 187 patients:
  - 110 had a positive GM-CSF autoantibody test.
  - 5 with a negative test had no underlying disease associated with secondary PAP.
- Evaluation of the family members of these 5 children identified 2 more children with undiagnosed PAP.
- One additional case was included in the analysis (a total of 8 patients).
- The serum GM-CSF concentration in these 8 children with GM-CSF autoantibody-negative PAP was higher than that of healthy family members and than that of unrelated healthy controls.
- Molecular analysis demonstrated that GM-CSF signaling was absent in 6 and severely reduced in 2 patients.
- The GM-CSF receptor β chain was detected in all patients, whereas the α chain was absent in 6 and abnormal in 2, paralleling the GM-CSF signaling defects.
- Genetic analysis revealed multiple distinct \textit{CSF2RA} abnormalities.
- All symptomatic patients responded well to whole-lung lavage therapy.

Conclusions:

- \textit{CSF2RA} mutations cause a genetic form of PAP presenting as insidious, progressive dyspnea in children.
- It can be diagnosed by a combination of characteristic radiologic findings and blood tests and treated successfully by whole-lung lavage.

**Background:**
- Serotonin (5-hydroxytryptamine; 5-HT) induces fibroblast proliferation via the 5-HTR$_{2A}$ and 5-HTR$_{2B}$ receptors.

**Purpose:**
- To determine the expression of 5-HT receptors in IPF and experimental lung fibrosis and to investigate the effects of therapeutic inhibition of 5-HTR$_{2A/B}$ signaling on lung fibrosis in vivo and in vitro.

**Methods and results:**
- **Quantitative RT-PCR**
  - Expression of 5-HTR$_{1A/B}$ and 5-HTR$_{2B}$ was significantly increased in the lungs of patients with IPF (n=12) and in those with non-specific interstitial pneumonia (NSIP, n=6) compared with transplant donors (n=12).
  - The expression of 5-HTR$_{2A}$ was increased specifically in IPF lungs but not in NSIP lungs.
- While 5-HTR$_{2A}$ protein largely localized to fibroblasts, 5-HTR$_{2B}$ localized to the epithelium.
- To assess the effects of 5HTR$_{2A/B}$ inhibition on fibrogenesis in vivo
  - Mice were subjected to bleomycin-induced lung fibrosis and treated with the 5-HTR$_{2A/B}$ antagonist terguride (or vehicle) in a therapeutic approach (days 14-28 after bleomycin).
  - Terguride-treated mice had significantly improved lung function and histology and decreased collagen content compared with vehicle-treated mice.
- Functional in vitro studies showed that terguride is a potent inhibitor of transforming growth factor β1- or WNT3a-induced collagen production.

**Conclusion:**
- The studies revealed an increased expression of 5-HTR$_{2A}$ specifically in IPF.
- Blockade of 5-HTR$_{2A/B}$ signalling by terguride reversed lung fibrosis and is thus a promising therapeutic approach for IPF.
Figure 2  Expression and localisation of the serotonin (5-HT) receptor 5-HTR$_{2A}$ in lung tissue from controls (transplant donors) and patients with idiopathic pulmonary fibrosis (IPF). Immunohistochemical staining was performed on tissue sections of donor lungs (left panels) and IPF lungs (right panels). Stainings are representative of four independent experiments using at least three different donor or IPF lung tissues. Scale bars indicate 100 μm. Arrows indicate positive staining of fibroblasts in IPF.

Figure 3  Expression and localisation of the serotonin (5-HT) receptor 5-HTR$_{2B}$ in lung tissue from controls (transplant donors) and patients with idiopathic pulmonary fibrosis (IPF). (A) Immunohistochemical stainings are representative of four independent experiments using at least three different donor or IPF lung tissues and two different primary antibodies. Scale bars indicate 100 μm. Arrows indicate positive staining of fibroblast in IPF, arrowheads highlight staining in bronchial and alveolar epithelial cells. (B) The mRNA levels of 5-HTR$_{2A}$ and 5-HTR$_{2B}$ were determined by qRT-PCR in primary human ATII cells (n=4) isolated from IPF lung tissue and compared with ATII cells from donor lungs. The results are plotted as fold change (2$^{\Delta\DeltaCT}$) of mRNA levels in IPF-derived vs donor-derived cells and presented as mean±SEM, *p<0.05.
II. ARTICLES FOR NOTATION ONLY
Neoplastic diseases


An excerpt from the course “The Surgical Pathology of Neoplastic Diseases” at Memorial Sloan-Kettering Cancer Center

The review
- Is based on the 2004 World Health Organization (WHO) Classification.
- Emphasizes the utility of **Ki-67 (MIB1)** in the diagnosis of lung neuroendocrine tumors, particularly in small biopsy and cytology.
  - Immunohistochemistry for Ki-67 (MIB1) is not part of the 2004 WHO criteria, but several recent studies suggest a utility for this marker, particularly in small biopsy and cytology specimens.
  - Ki-67 proliferation rates based on the compilation of several recent studies (Table 4):
    - TC: less than 2%.
    - AC: less than 20% (typical rate is 10%)
    - SCLC and LCNEC: significantly higher than 20% (typical rate for SCLC is 60%–100%).

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Specimen Type</th>
<th>N</th>
<th>Percentage of Ki-67 (MIB1)-Positive Cells, Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi et al, 2004</td>
<td>Resection</td>
<td>57</td>
<td>0.5</td>
</tr>
<tr>
<td>Arliser et al, 2001</td>
<td>Resection</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Igarashi et al, 2004</td>
<td>Resection</td>
<td>111</td>
<td>1.3 (0.3–2.3)</td>
</tr>
<tr>
<td>Pelosi et al, 2005</td>
<td>Resection</td>
<td>220</td>
<td>2.3</td>
</tr>
<tr>
<td>Iyoda et al, 2004</td>
<td>Resection</td>
<td>27</td>
<td>1 (0–6)</td>
</tr>
<tr>
<td>Pelosi et al, 2003</td>
<td>Resection</td>
<td>11</td>
<td>32 (20–61)</td>
</tr>
<tr>
<td>Costes et al, 1995</td>
<td>Resection</td>
<td>47</td>
<td>0.45</td>
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<tr>
<td>Pelosi et al, 2005</td>
<td>Biopsy</td>
<td>15</td>
<td>0.5 (0–1)</td>
</tr>
<tr>
<td>Aslan et al, 2005</td>
<td>Biopsy and resection</td>
<td>22</td>
<td>1 (0–10)</td>
</tr>
<tr>
<td>Lin et al, 2003</td>
<td>Cytology</td>
<td>63</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

**Weighted Mean (Range) for the above studies**
- TC: 1.5 (0–2.3)
- AC: 7.7 (1–17)
- LCNEC: 46 (20–90)
- SCLC: 64 (25–96)

Abbreviations: AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma; TC, typical carcinoid.

An excerpt from the course ‘‘The Surgical Pathology of Neoplastic Diseases’’ at Memorial Sloan-Kettering Cancer Center

**Lung:**
- Sarcomatoid carcinomas
  - Pleomorphic carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Pleuropulmonary blastomas

**Pleura:**
- Malignant mesothelioma
  - Sarcomatoid
  - Desmoplastic
- Solitary fibrous tumor
- Desmoid tumor

Background:
- **c-Met**
  - Important in the pathogenesis and spread of several forms of lung cancer.
  - Multiple c-Met inhibitors are undergoing clinical trials.
- **PAX5**
  - Has been shown to upregulate c-Met in small cell lung carcinoma (SCLC).
  - Coinhibiting PAX5 and c-Met had a synergic effect in killing tumor cells.
- **Paxillin**
  - Downstream target of activated c-Met.
  - Its activation leads to enhanced cell motility and tumor spread.

Purpose:
- To investigate the expression patterns of **PAX5, paxillin, c-Met, and phosphorylated c-Met** in pulmonary neuroendocrine tumors.

Methods:
- Tissue microarrays
  - 38 typical carcinoids
  - 6 atypical carcinoids
  - 34 SCLCs
  - 11 large cell neuroendocrine carcinomas
- Immunohistochemistry

Results:
- Most of the 4 tumor types expressed c-Met, phosphorylated c-Met, and paxillin.
- PAX5 was frequently expressed in atypical carcinoids, SCLCs, and large cell neuroendocrine carcinomas but tended to be negative in typical carcinoids.
- Coexpression of PAX5 with c-Met or phosphorylated c-Met was present in most of the atypical carcinoids, SCLCs, and large cell neuroendocrine carcinomas.
- Significant correlation between PAX5 and paxillin was detected in SCLCs and large cell neuroendocrine carcinomas but not in carcinoid tumors.

Conclusions:
- The frequent coexpression of PAX5 with c-Met or phosphorylated c-Met in intermediate-grade and high-grade neuroendocrine tumors supports the therapeutic strategy of coinhibiting these proteins.
- The discrepancy between high-grade and low-grade neuroendocrine tumors in PAX5/paxillin expression correlation may be due to the different underlying molecular genetics of these tumors.

Postgraduate Education Corner - CHEST IMAGING AND PATHOLOGY FOR CLINICIANS

Diagnosis: Pleural epithelioid hemangioendothelioma


Background:
• Ovine pulmonary adenocarcinoma (OPA, also known as Jaagsiekte) is a contagious lung cancer of sheep caused by a betaretrovirus, Jaagsiekte sheep retrovirus (JSRV).

Purpose:
• To investigate the hypothesis that a retrovirus might be present in human lung adenocarcinoma.

Methods:
• The authors examined specimens from patients with lung cancer for evidence of retroviral infection by immunohistochemistry, reverse transcriptase–polymerase chain reaction, immunoblotting and cDNA library screening.

Results:
• Thirty-eight percent of the tumor samples analyzed was positive by immunohistochemistry for Gag-related antigen of Jaagsiekte sheep retrovirus.
• However, this antigen was not detected by immunoblotting using the same antiserum.
• In addition, plasma samples from the patients did not contain antibodies reacting with Gag proteins from Jaagsiekte sheep retrovirus or other betaretroviruses on immunoblots.
• Reverse transcriptase–polymerase chain reaction identified the expression of endogenous betaretroviruses in tumor tissue and in normal lung tissue, but no specific provirus was associated with tumor.
• Expression library screening did not identify the Gag-reactive antigen.

Conclusions:
• This study has confirmed the expression of a Jaagsiekte sheep retrovirus Gag–related antigen in some human lung tumors but additional evidence of betaretroviral infection was not obtained.
• While these data do not rule out a role for a retrovirus in human pulmonary adenocarcinomas, they suggest that, if such a virus is present, it is unrelated to known betaretroviruses.
Purpose:
- To examine copy number alterations in an inflammatory myofibroblastic tumor (IMT) case.

Methods:
- The authors used a 30K whole-genome human oligoarray with approximately 100 Kb resolution.
- RNA expression of putative cancer-related genes located in the chromosomal altered regions was assessed by qRT-PCR.

Results:
- The authors identified
  - seven copy number gained regions
  - seven lost regions
  - nine amplifications
  - six homozygous deletions
- In high-level amplification regions RNA expression of four potential cancer-related genes was examined: GSTT1, ESR1, EVI1 and MITF; among them, GSTT1 and ESR1 were significantly up-regulated, but EVI1 and MITF showed insignificant elevation of RNA expression.
- In homozygously deleted regions, RNA levels of putative tumor suppressors, SEMA3B, SEMA3F and SULT2A1, were significantly repressed.

Conclusions:
- Most of the putative cancer-related genes identified in this study are supposedly novel in IMT.

Background:
• TLE1, which plays an important role in Wnt pathway, has been shown to be a specific marker for synovial sarcoma.

Purpose:
• To evaluate TLE1 expression in malignant mesotheliomas.

Methods:
• 29 malignant mesotheliomas
• Immunohistochemical analysis
  o TLE1
  o Factors related to the Wnt pathway including β-catenin and cyclin D1
  o Mesothelioma markers including calretinin, HBME-1, cytokeratin 5/6, and thrombomodulin

Results:
• TLE1 was variably expressed in 28 malignant mesotheliomas regardless of histomorphological subtype with >25% of positive cells in 20 cases (69.0%).

Conclusion:
• The study showed no or limited value of the immunohistochemical TLE1 expression in distinguishing malignant mesothelioma and synovial sarcoma.
Non-neoplastic diseases


Report of a case:
- A case of LAM in a young lady is presented.
- It was complicated with pleural and peritoneal chylous effusions.
- The diagnosis was first made on a retroperitoneal lymph node biopsy.
- The patient had a prolonged prior history of respiratory problems owing to lung involvement, and died 2 years after diagnosis.

Discussion:
- **LAM**
  - A systemic, progressive, and fatal condition affecting almost exclusively women in their reproductive years.
  - May involve the lungs and the axial lymphatics and lymph nodes of the thorax and retroperitoneum.
  - Most often occurs as a sporadic disease, but also occurs in women with tuberous sclerosis complex (TSC) (syndromic LAM).
  - There are no pathologic differences between sporadic and syndromic LAM.
- **Sporadic LAM**
  - A rare disease with prevalence of approximately 1 to 2 cases per million women in the United States and among populations of white descent, and is even rarer among Asian and African individuals.
  - Often found in association with renal angiomyolipoma, the most common sign of TSC, but LAM associated with angiomyolipoma does not define TSC.
  - Although LAM is not diagnostic for TSC either in isolation or in association with angiomyolipoma, still it is considered by some researchers as an incomplete expression (forme fruste) of TSC.
- **Syndromic LAM**
  - Affects 4% to 5% of women with TSC.
Doxtader EE, Mukhopadhyay S, Katzenstein A-LA. Core needle biopsy in benign lung lesions: pathologic findings in 159 cases. Hum Pathol. 2010;41:1530–1535

Purpose:
- To review the pathologic findings in 159 core needle biopsies showing benign changes.

Results:

<table>
<thead>
<tr>
<th>Specific diagnoses</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing granulomatous inflammation</td>
<td>45</td>
</tr>
<tr>
<td>No organism identified</td>
<td>30</td>
</tr>
<tr>
<td>Organism identified</td>
<td>15</td>
</tr>
<tr>
<td>Histoplasma (10)</td>
<td></td>
</tr>
<tr>
<td>Coccioides (2)</td>
<td></td>
</tr>
<tr>
<td>Mycobacteria (2)</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus (2)</td>
<td></td>
</tr>
<tr>
<td>Scar</td>
<td>28</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>13</td>
</tr>
<tr>
<td>Benign neoplasm</td>
<td>11</td>
</tr>
<tr>
<td>Hamartoma</td>
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</tr>
<tr>
<td>Solitary fibrous tumor</td>
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<tr>
<td>Schwannoma</td>
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<tr>
<td>Non-necrotizing granulomatous inflammation</td>
<td>8</td>
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<tr>
<td>No organism identified</td>
<td>5</td>
</tr>
<tr>
<td>Organism identified</td>
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</tr>
<tr>
<td>Cryptococcus (2)</td>
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</tr>
<tr>
<td>Fungal hyphae (1)</td>
<td></td>
</tr>
<tr>
<td>Other specific diagnoses</td>
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<td>Abscess</td>
<td>5</td>
</tr>
<tr>
<td>Nodular amyloidosis</td>
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<tr>
<td>Intrapulmonary lymph node</td>
<td>3</td>
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<tr>
<td>Mycetoma</td>
<td>2</td>
</tr>
<tr>
<td>Invasive fungal pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcal pneumonia</td>
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</tr>
<tr>
<td>Nonspecific diagnoses</td>
<td>24 (15%)</td>
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<tr>
<td>Interstitial fibrosis and chronic inflammation</td>
<td>16</td>
</tr>
<tr>
<td>Necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Acute and/or chronic inflammation</td>
<td>2</td>
</tr>
<tr>
<td>Intra- alveolar fibrin</td>
<td>2</td>
</tr>
<tr>
<td>Organizing hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Nonrepresentative biopsies</td>
<td>13 (8%)</td>
</tr>
</tbody>
</table>

Conclusion:
- The findings confirm that core needle biopsy is an accurate method of diagnosing benign lung lesions, yielding specific diagnoses in the majority.

Purpose:
• To investigate incipient inflammatory changes in the lungs of burn victims.

Methods:
• 40 forensic autopsy cases of burn victims that had died within 1 h after fire exposure.
• 48 autopsy cases in three control groups.
• Immunohistochemical studies of lung tissue using antibodies against:
  o Tumour necrosis factor a (TNF-α)
  o Interleukin-8 (IL-8)
  o Inter-cellular adhesion molecule 1 (ICAM-1)

Results:
• The lungs of burn victims showed a significantly higher extent of intra-alveolar oedema than the other groups.
• Immunohistochemically, macrophages in all groups mostly showed a distinct expression of TNF-α, but not of IL-8 or ICAM-1.
• Intravascular erythrocytes often showed a positivity of TNF-α that was strongest in the group of burn victims and differed significantly from all the control groups.

Conclusions:
• In burn victims with short survival times of ≤1 h after fire exposure, the immunohistochemical expression profiles of TNF-α, IL-8 and ICAM-1 in the lungs were not altered enough to prove an instant inflammatory reaction in these cases.
• Nevertheless, the positive reaction of TNF-α in erythrocytes of burn victims may indicate the beginning of a non-specific immune response to fire-induced inhalation trauma.

Purpose:
- To describe the postmortem findings of eight confirmed cases of influenza A/H1N1 in a medical examiner setting.

Results:
- **Clinical characteristics:**
  - All cases were males between 6 months and 54 years of age.
  - All adult patients had a body mass index from 31 to 49.8 kg/m2.
  - Five cases had comorbid conditions including one case with sleep apnea and mental retardation, three cases with chronic ethanolism, and one case with thymoma, sarcoidosis, and myasthenia gravis.
  - All patients presented with severe flu-like symptoms; yet, only five were febrile.
  - Rapid influenza diagnostic tests were performed in three cases by primary-care physicians, two of which were negative.
  - None of the patients received antiviral medication. The average disease duration time was 8.2 days (3–14 days).

- **Histopathological findings:**
  - Tracheitis
  - Necrotizing bronchiolitis
  - Alveolitis
  - Intra-alveolar hemorrhage
  - Hyaline membranes, both in focal and in a diffuse distribution

Conclusions:
- These histopathological findings at autopsy along with a clinical history of flu-like symptoms should raise suspicion for influenza A/H1N1 infection, and postmortem analysis by the reverse transcription-polymerase chain reaction (RT-PCR) is recommended for an accurate diagnosis.


CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Pathological Diagnosis: Coccidioidomycosis.