ARTICLES FOR DISCUSSION:


**Background:**
- Large cell carcinomas (LCCs) of the lung are heterogeneous and may be of different cell lineages.
- Besides immunohistochemical studies and gene profiling, microRNA analysis seems to be a new promising diagnostic tool for lung cancer. Lebanony et al and Bishop et al reported that the relative quantification of miRNA-205, in comparison with 2 other small noncoding RNAs (the “oncomicroRNA” microRNA-21 and the housekeeping small nuclear [sn]RNA U6, using the microRNA sample score [mRSS] method) correctly distinguishes lung squamous cell carcinoma (SQCC) from adenocarcinoma (ADC).

**Methods:**
- 56 surgically resected lung tumors classified as LCC on the basis of pure morphologic grounds
- Panel of immunophenotypic markers:
  - ADC-specific
    - thyroid transcription factor-1
    - cytokeratin 7
    - napsin A
  - SQCC-specific
    - p63
    - cytokeratin 5
    - desmocollin 3
    - Δnp63
- Quantitative analysis of miRNA-205 (miRNA sample score [mRSS])
  - The miR205, miR21, and U6 snRNA were measured by quantitative RT-PCR in triplicate.
  - Lebanony et al used an mRSS of 2.5 as the threshold for separating SQCCs from nonsquamous carcinomas. Cancers with mRSSs below this threshold were classified as SQCCs, and those with scores above this threshold were classified as ADCs.

**Results:**
- Based on immunoprofiles 19 (34%) of the cases were reclassified as ADC and 14 (25%) as SQCC; 23 (41%) of the cases were unclassifiable.
Of these 23 cases, 18 were classified as ADC and 5 as SQCC according to the mRSS.

Conclusions:
- The data show that an extended panel of immunohistochemical markers can reclassify around 60% of LCCs as ADC or SQCC.
- However, a relevant percentage of LCCs may escape convincing immunohistochemical classification, and mRSS could be used for further typing, but its clinical relevance needs further confirmation.


Background:
- Deletion of exon 19 of the epidermal growth factor receptor (EGFR) and mutation of exon 21 are the most common EGFR mutations and predict higher response to EGFR tyrosine kinase inhibitors (TKI).
- Accumulating data show clinical differences in both response and survival between these two EGFR mutations.
- This study investigated the clinical impact of EGFR exon 19 deletion and L858R mutation by retrospectively analysing the clinical outcome of patients with advanced non-small-cell lung cancer (NSCLC) treated with EGFR TKI.

Methods:
- Patients harbouring EGFR exon 19 deletion or L858R mutations and who had received gefitinib or erlotinib treatment were identified.
- The response rate (RR), progression-free survival (PFS) and overall survival (OS) were determined for the two groups.
- EGFR mutation was determined by PCR-based direct sequencing.

Results:
- The study indentified 87 patients harbouring EGFR exon 19 deletion (n=61) or L858R mutation (n=26) who were treated with either gefitinib (n=83) or erlotinib (n=4).
- Patients with exon 19 deletion had significantly longer PFS, compared with patients with L858R mutation (9.3 vs 6.9 months, p=0.02).
- In a multivariate Cox regression model, EGFR exon 19 deletion was independently predictive of longer PFS (p=0.02).
- However, no significant differences in RR (64% vs 62%, p=0.83) and OS (17.7 vs 20.5 months, p=0.65) were observed between these two mutations.
Conclusion:
- While no significant difference in OS was observed between EGFR exon 19 deletion and L858R mutation, EGFR exon 19 deletion was predictive of longer PFS following EGFR TKI treatment in patients with advanced NSCLC.


Background/Methods:
- In 1999, Nicholson et al reported 2 cases which were then classified as low-grade “malignant myxoid endobronchial tumors”, comprising lobulated growths of cells in reticular or cord-like patterns within abundant myxoid stroma.
- The authors now describe 8 additional primary pulmonary tumors with this morphology and provide molecular genetic data for a recurrent, nonrandom gene fusion
- The tumors are now renamed as “primary pulmonary myxoid sarcoma” (PPMS).

Results:
- The patients [7 female, 3 male; aged 27 to 67 y (mean, 45 y)] presented with local or systemic symptoms (n=5), symptoms from cerebral metastasis (1), or incidentally (2).
- Follow-up of 6 patients showed that 1 with brain metastasis died shortly after primary tumor resection, 1 developed a renal metastasis but is alive and well, and 4 are disease free after 1 to 15 years.
- All tumors involved pulmonary parenchyma, with a predominant endobronchial component in 8 and ranged from 1.5 to 4 cm.
- Microscopically:
  - They were lobulated and composed of cords of polygonal, spindle, or stellate cells within myxoid stroma, morphologically reminiscent of extraskeletal myxoid chondrosarcoma.
  - Four cases showed no or minimal atypia, 6 showed focal pleomorphism, and 5 had necrosis.
Mitotic indices varied, with most tumors not exceeding 5/10 high-power fields.

- Tumors were immunoreactive for only vimentin and weakly focal for epithelial membrane antigen.
- 7 of 9 tumors: EWSR1-CREB1 fusion by reverse transcription-polymerase chain reaction and direct sequencing.
- 7 of 10 tumors: EWSR1 rearrangement by fluorescence in situ hybridization.

Conclusions:

- PPMS is a specific tumor arising in the lung that has distinct histologic and genetic features.
- The characteristic gene fusion is novel to this site and tumor type, although it has previously been described in 2 other soft tissue sarcomas (clear cell sarcoma-like tumors of the gastrointestinal tract and angiomatoid fibrous histiocytomas).


Background:

- Patients with interstitial lung disease (ILD) may have features of an autoimmune disorder that do not meet the diagnostic criteria for connective tissue diseases.
- The authors determined the prevalence and characteristics of autoimmune-featured ILD (AIF-ILD) and compared these with those of idiopathic pulmonary fibrosis (IPF) and known connective tissue disease-related ILD (CTD-ILD).

Methods:

- Patients with ILD who did not meet the American College of Rheumatology (ACR) criteria for a connective tissue disease were defined as having AIF-ILD if they had a sign or symptom suggestive of a connective tissue disease and a serologic test reflective of an autoimmune process.

<table>
<thead>
<tr>
<th>Symptoms (One or More of the Following)</th>
<th>Serologic Test (One or More Positive Result of the Following)</th>
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<tbody>
<tr>
<td>Dry eyes/dry mouth</td>
<td>Antinuclear antibody titer ≥ 1:160</td>
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<tr>
<td>Gastroesophageal reflux</td>
<td>Rheumatoid factor</td>
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<tr>
<td>Weight loss</td>
<td>Aldolase</td>
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<tr>
<td>Leg/foot swelling</td>
<td>Anti-Ro antibody</td>
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<tr>
<td>Joint pain/swelling</td>
<td>Anti-La antibody</td>
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<td>Rash</td>
<td>Anti-neutrophil cytoplasmic antibody</td>
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<tr>
<td>Photosensitivity</td>
<td>Creatine kinase</td>
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<tr>
<td>Dysphagia</td>
<td>Anti-double-stranded DNA</td>
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<tr>
<td>Hand ulcers</td>
<td>Anti-Sc1-70</td>
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<tr>
<td>Mouth ulcers</td>
<td>Anti-ribonucleoprotein antibody</td>
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<td>Raynaud phenomenon</td>
<td>Anti-Smith antibody</td>
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<tr>
<td>Morning stiffness</td>
<td>Anti-cyclic citrullinated peptide antibody</td>
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<tr>
<td>Proximal muscle weakness</td>
<td>Anti-Jo-1 antibody</td>
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</table>
• Currently, these patients are considered to have an idiopathic interstitial pneumonia, although it has been suggested that these patients may have an undifferentiated connective tissue disease (UCTD). However, UCTD as described in the rheumatology literature is mild in nature 6-8 and has a low prevalence of ILD (1%).

• Clinical characteristics, high-resolution CT images, and lung biopsy specimens were analyzed and compared with those of patients with IPF and CTD-ILD. Survival was evaluated using a Kaplan-Meier curve.

Results:
• Two hundred subjects completed the questionnaire and serologic testing.
• AIF-ILD was identified in 32%, IPF in 29%, and CTD-ILD in 19%.
• Gender, age, and race differed among groups (P < .01).
• Sixty-two percent of patients with AIF-ILD had a typical usual interstitial pneumonia (UIP) pattern on CT images.
• In 31 patients with AIF-ILD, lung biopsy specimens showed UIP in 81% and nonspecific interstitial pneumonia in 6%.

Patients with AIF-ILD and IPF had similar survival, worse than those with CTD-ILD (P < .01).

Antinuclear antibody (ANA) titers ≥ 1:1280 were associated with improved survival in patients with AIF-ILD (P = .02).

Conclusions:
• A UIP pattern on CT images and histopathology is common in AIF-ILD.
• Although survival for patients with AIF-ILD is poor, ANA titers ≥ 1:1280 are associated with improved survival.

Background:
- Ten years ago a bioterrorism event involving Bacillus anthracis spores captured the nation's interest, stimulated extensive new research on this pathogen, and heightened concern about illegitimate release of infectious agents.
- Sporadic reports have described rare, fulminant, and sometimes fatal cases of pneumonia in humans and nonhuman primates caused by strains of Bacillus cereus, a species closely related to Bacillus anthracis.
- The authors describe a case of rapidly progressive, fatal, anthrax-like pneumonia in a patient residing in rural Texas.

Methods:
- The genome of the causative strain was characterized within days of its recovery from antemortem cultures using next-generation sequencing.
- Immunohistochemistry was performed on tissues obtained at autopsy with antibodies directed against virulence proteins of B anthracis and B cereus.

Results:
- The infection was caused by a previously unknown strain of B cereus that was closely related to, but genetically distinct from, B anthracis.
- The strain contains a plasmid similar to pXO1, a genetic element encoding anthrax toxin and other known virulence factors.
- Immunohistochemistry demonstrated that several homologs of B anthracis virulence proteins were made in infected tissues, likely contributing to the patient's death.

Conclusion:
- Rapid genome sequence analysis permitted the authors to genetically define this strain, rule out the likelihood of bioterrorism, and contribute effectively to the institutional response to this event.
ARTICLES FOR NOTATION:

Neoplastic:


Background:
- There is growing evidence that lung adenocarcinoma and squamous cell carcinoma (SQCC) have distinct oncogenic mutations and divergent therapeutic responses, which is driving the heightened emphasis on accurate pathologic subtyping of non-small cell lung carcinoma (NSCLC).
- The relative feasibility and accuracy of NSCLC subtyping by small biopsy versus cytology is not well established, particularly in current practice where immunohistochemistry (IHC) is becoming routinely used to aid in this distinction.

Methods:
- Concurrent biopsy and cytology specimens obtained during a single procedure and diagnosed as NSCLC during a 2-year period (n = 101) were reviewed.
- Concordance of diagnoses in the two methods was assessed. Accuracy was determined based on subsequent resection or autopsy diagnosis (n = 21) or IHC for thyroid transcription factor 1 and p63 on a subset of cases (n = 43).

Results:
- The distribution of definitive versus favored versus unclassified categories (reflecting the degree of diagnostic certainty) was similar for biopsy (71% versus 23% versus 6%, respectively) and cytology (69% versus 19% versus 12%, respectively), p = 0.29.
- When results from paired specimens were combined, the rate of definitive diagnoses by at least one method was increased to 84% and the unclassified rate was decreased to 4%.
- NSCLC subtype concordance between biopsy and cytology was 93%.
- Kappa coefficient (95% confidence interval) for agreement between methods was 0.88 (0.60-0.89) for adenocarcinoma and 0.76 (0.63-0.89) for SQCC.
- In pairs with discordant diagnoses (n = 7) the correct tumor type was identified with a similar frequency by biopsy (n = 4) and cytology (n = 3).
- Factors contributing to mistyping were poor differentiation, necrosis, low cellularity, and lack of supporting IHC.
- All concordant diagnoses for which verification was available (n = 57) were correct.
- IHC was used more frequently to subtype NSCLC in biopsy than cytology (32% versus 6%; p = 0.0001).

Conclusions:
- Small biopsy and cytology achieve comparable rates of definitive and accurate NSCLC subtyping, and the optimal results are attained when the two modalities are considered jointly.
- The lower requirement for IHC in cytology highlights the strength of cytomorphology in NSCLC subtyping.
Whenever clinically feasible, obtaining parallel biopsy and cytology specimens is encouraged.


**Background:**
- Emerging targeted lung cancer therapies require the accurate morphologic subclassification of non-small cell lung cancer (NSCLC), even in scant and distorted specimens obtained by transthoracic needle aspiration (TTNA).
- MicroRNAs (miRNAs) are small noncoding genes recently reported as useful in differentiating squamous cell carcinoma (SCC) from adenocarcinoma (AD) in resected tumor specimens.
- The authors investigated the ability of miRNAs to do so in TTNA specimens.

**Methods:**
- Smears, immunocytochemistry slides, and corresponding cell blocks of 31 NSCLC TTNA specimens were retrieved and classified as AD or SCC based on their cytologic features and immunocytochemical profiles.
- Data on EGFR and K-RAS mutational status were available for all cases of AD.
- The authors quantified the hsa-let-7 family and hsa-miR-205 by quantitative reverse transcription-polymerase chain reaction and compared the miRNA expression levels in AD and SCC using Student t test.

**Results:**
- Eighteen cases were classified as AD and 13 as SCC by light microscopy and immunocytochemistry.
- miRNA expression profiles demonstrated considerable, statistically significant differences between AD and SCC, showing an upregulation of hsa-let-7a, hsa-let-7b, hsa-let-7c, hsa-let-7f, hsa-let-7g, hsa-let-7i, and hsa-miR-98 and a downregulation of hsa-miR-205 in AD specimens (all P < .05; t test).

**Conclusions:**
- Profiling the hsa-let-7 family and hsa-miR-205 is a promising method for differentiating AD from SCC, even in such small specimens as transthoracic aspirates. Subject to the validation of these findings in further, larger studies, this could prove to be a reliable, standardizable tool for the subclassification of NSCLC.

Background/Methods:
- The authors report 5 cases of pulmonary salivary gland-type tumors with features of carcinoma ex pleomorphic adenoma.

Results:
- Patient ages ranged from 44 to 71 years (mean, 53.8 years); 4 patients were men and 1 was a woman.
- In all 5 cases, the lesions were associated with the bronchial system.
- None of the patients had a history of a head and neck salivary gland neoplasm.
- Histologically the lesions were invasive tumors containing:
  - malignant myoepithelial elements and
  - duct-like structures embedded in a benign chondromyxoid stroma.
- Areas reminiscent of residual pleomorphic adenoma were noted in 2 cases.
- Follow-up for 3 patients:
  - 2 died 22 and 54 months after diagnosis and
  - 1 was alive 20 months after diagnosis.

Conclusions:
- The cases are suggestive of carcinoma ex pleomorphic adenoma, an entity that has not been well documented in the bronchopulmonary system.


Background:
- Malignant cartilaginous tumors of the lung are unusual, and although their occurrence has been reported in the literature in some cases, their separation from other benign cartilaginous tumors of the lung can be very difficult.

Methods:
- Four cases of primary chondrosarcomas of the lung are presented.

Results:
- The patients are 2 men and 2 women between the ages of 51 and 69 years.
- Clinically, the most common symptoms were chest pain, dyspnea, and cough.
- Two tumors were centrally located, whereas 2 tumors were peripheral.
- Complete surgical resection was accomplished in all the patients.
- Histologically, 2 tumors were low grade of the hyaline type, whereas 2 tumors were predominantly myxoid chondrosarcomas.
- In the 2 myxoid chondrosarcomas immunohistochemical studies for keratin, desmin, smooth muscle actin, and CD31 were negative, whereas S-100 protein showed focal positive staining in both cases.
Follow-up showed that one patient with low-grade tumor was alive and well at 36 months, whereas one patient with myxoid chondrosarcoma died 45 days after diagnosis because of surgical complications.

Two additional patients were lost to follow-up.

Conclusions:

- The study highlights the ubiquitous distribution of chondrosarcomas and the histopathologic spectrum that these tumors may show when occurring in the lung.


Background:

- There is limited evidence regarding the effectiveness of multidisciplinary team (MDT) meetings in lung cancer.
- The objective of this study was to compare the patterns of care for patients with newly diagnosed lung cancer who were presented at a lung cancer MDT meeting with the patterns of care for patients who were not presented.

Methods:

- All patients who had lung cancer newly diagnosed in South West Sydney (SWS) between December 1, 2005, and December 31, 2008, were identified from the local Clinical Cancer Registry.
- Patient and tumor characteristics and treatment receipt were compared between patients who were and were not presented at MDT meetings. A logistic regression model was constructed to determine predictors for receiving treatment and survival.

Results:

- In total, there were 988 patients, including 504 patients who were presented at MDT meetings and 484 who were not presented at MDT meetings.
- The median patient age was 69 years and 73 years in the MDT group and the non-MDT group, respectively (P < .01).
- There was no pathologic diagnosis for 13% of non-MDT patients compared with 4% of MDT patients (P < .01).
- Treatment receipt for MDT patients versus non-MDT patients was 12% versus 13%, respectively, for surgery (P value nonsignificant); 66% versus 33%, respectively, for radiotherapy (P < .001); 46% versus 29%, respectively, for chemotherapy (P < .001); and 66% versus 53%, respectively, for palliative care (P < .001).
- In patients with good performance status, the MDT group had significantly better receipt of radiotherapy among patients with stage I through IV nonsmall cell lung cancer (NSCLC) and had significantly better receipt of chemotherapy among patients with stage IV NSCLC.
- MDT discussion was
  - an independent predictor of receiving radiotherapy, chemotherapy, and referral to palliative care but
Conclusions:

- MDT discussion was associated with better treatment receipt, which potentially may improve quality of life for patients with lung cancer.
- However, it did not improve survival.

Non-neoplastic:


Background:

- During the past 2 decades, silica sand has been used widely in sandblasting denim in Turkey, which has resulted in an epidemic of silicosis.
- This study was conducted to summarize the clinical outcomes of formerly healthy young people who became disabled or died because of working in the textile industry.

Methods:

- The medical records of patients with silicosis due to denim sandblasting who were seen at the authors’ institution between 2001 and 2009 were reviewed.
- Follow-up data were assessed. Compensation and vital status of patients were determined, and survival analysis was performed.

Results:

- Thirty-two male patients diagnosed with silicosis due to denim sandblasting over an 8-year period were identified.
- Mean age was 31.5 years.
- They worked as denim sandblasters for a mean 66.4 h/wk for a median 28.5 months.
- Their mean cumulative exposure time to silica sand was 12,957 h.
- The median follow-up period was 29 months (range 3-101 months).
- The median latency period (time elapsed between initial exposure and diagnosis) was 5.5 years (range 2-14 years).
- Six of the followed patients (19%) died of progressive massive fibrosis.
- Nine of the patients (28%) were compensated because of silicosis.
- Just two patients with silicosis received compensation before they died.
- The mean survival rate was 78 months.
- The estimated 5-year survival rate was 69% for denim sandblasters with silicosis.

Conclusions:

- Silicosis in young individuals after exposure in the textile sector suggests a lack of awareness of the hazards of silica outside of the traditional occupations associated with silicosis in Turkey.
- Death from silicosis in young people suggests overexposure and unsafe working conditions as a result of a lack of control.

**Background:**
- To elucidate the nature of capillary alterations in severe pulmonary venous congestion (SPVC).

**Methods:**
- Post-mortem lungs from 52 patients with left-sided cardiac failure were examined, including 31 cases of valvular heart disease and 21 cases of cardiomyopathy.

**Results:**
- Six post-mortem lungs (six of 52, 11.5%) had patchy lesions composed of markedly widened alveolar walls containing numerous dilated capillaries. These features mimicked pulmonary capillary haemangiomatosis (PCH).
- Moreover, one (one of 52, 1.9%) lung showed numerous fibrous micronodules containing capillaries with or without ossification, associated with prominent capillary sprouts, suggesting capillary varicose changes.
- No pathological features suggesting plexiform angiopathy or veno-occlusive disease were found.
- Ultrastructural examination revealed occasional interposition of swollen endothelial cells in the thickened basement membranes of the pulmonary capillaries.

**Conclusion:**
- PCH-like lesions can occur infrequently as an incidental finding in SPVC, rarely accompanying ossifying fibrocapillary micronodules.
- These lesions are considered to be a secondary form of PCH, representing severely tortuous and proliferative capillary changes rather than neoplasia.


**Background:**
- Pneumoconiosis induced by non-crystalline silica is considered rare, although silicosis resulting from contact with crystalline silica is a well-known hazard associated with progressive pulmonary fibrosis.

**Methods:**
- The authors describe a patient with pneumoconiosis induced by diatomaceous earth composed of amorphous silica detected by two-dimensional imaging of chemical elements.

**Results:**
- The histology revealed that the disease was characterized by a granulomatous reaction in the lung.
A large number of macrophages laden with yellow and black pigments accumulated in alveolar spaces and were incorporated into the interstitium.

Bronchiolar walls were destroyed by palisading macrophages.

Immunohistochemistry showed that cyclooxgenase-2, an antifibrogenic mediator, was intensely expressed in the macrophages compared with macrophages in control lungs.

No birefringent material was found in the tissues.

When two-dimensional analysis of chemical elements was performed using an electron probe microanalyzer with a wavelength-dispersive spectrometer, the resultant fine mapping of silicon and oxygen on the tissue indicated that the pigments phagocytosed by macrophages corresponded to amorphous silica.

Conclusion:

Two-dimensional analysis of elements is useful in correlating the presence of chemical elements with histological changes.