DISCUSSION ARTICLES


ARTICLES FOR NOTATION

Techniques:


Hoffmann et al. Human skin keratins are the major proteins in exhaled breath condensate. Eur Respir J. 2008;31:380-4.


(Described in last months journal club)

Neoplasia:


(Described in last months journal club)

(Described in last months journal club)

(Described in last months journal club)

(Described in last months journal club)
**Interstitial Lung Disease:**


(Described in last months journal club)

(Described in last months journal club)

(Described in last months journal club)

(Described in last months journal club)

**Airway Inflammation: Chronic Obstructive Pulmonary Disease/Asthma:**


(Described in last months journal club)

(Described in last months journal club)
Infection:


Sakkour et al. A 56-Year-Old Woman With COPD and Multiple Pulmonary Nodules. Chest 2008; 133:566-569. (Described in last months journal club)


Pulmonary Vascular Disease:


Transplantation


**Rationale:** Desquamative interstitial pneumonia (DIP) is a rare pattern of diffuse parenchymal lung disease known to overlap with respiratory bronchiolitis-interstitial lung disease (RB-ILD). The clinical features of DIP have not been well studied.

**Objective:** To review biopsy-proven cases of DIP to investigate further the clinical, imaging and histological features of this disease.

**Methods:** Retrospective study which identified 20 patients considered to have classical features of DIP on lung biopsy (19 men, one woman, mean age (SD) 54 (11) y). Clinical features, BAL data, radiological findings, pathological findings other than criteria, effect of therapy and outcome were examined. The pathological changes were assessed semiquantitatively as normal, mild, moderate or severe. In the available biopsy material, the margin between the regions involved by DIP and adjacent lung was assessed as: abrupt transition, gradual transition, or not evaluable because of diffuse involvement of the specimen. Pathological changes assessed:

- the degree of alveolar septal/interstitial fibrosis
- architectural destruction
- cyst formation: differed from honeycombing in that they tended to lack bronchiolar metaplasia and had a much thinner fibrous wall.
- intra-alveolar organization.
- Alveolar septal fibrosis and cyst formation were scored as: panlobular, centrilobular, subpleural.

**Results:** All male subjects were smokers (current 17, ex 2).

**BAL:** 17 cases - revealed marked eosinophilia (mean 18%) and moderate neutrophilia (mean 11%).

<table>
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<th>Table 2. Bronchoalveolar lavage data for 17 cases and normal values</th>
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<tr>
<td>Patient data</td>
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<tr>
<td>Recovery % (mean ± SD), n = 12</td>
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<td>Recovered cells (mean ± SD), n = 17</td>
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<td>Macrophages (mean ± SD)</td>
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<td>Lymphocytes (mean ± SD)</td>
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<td>Eosinophils (mean ± SD, median, range)</td>
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<td>Neutrophils (mean ± SD, median, range)</td>
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**Radiology:** Bilateral ground-glass opacities in 70%, middle and lower lung field dominancy (70%) and only 10% showed volume loss. CT in 17 patients showed peripheral involvement in all cases with a clear margin in 64%. Tiny thin-walled cysts in
35% of cases in the ground-glass areas in 64% of cases. Honeycombing was noted in 12% of cases. Additionally, pathological features: a distinct lobular distribution (70%) (with differences in the degree of alveolar septal interstitial fibrosis between the lobules in 65% and an abrupt transition to relatively normal lung in 25%); architectural destruction (70%); cyst formation (55%). All but one case showed mildly increased tissue eosinophils, far short of the numbers seen in CEP. Of note was the fact that when tissue uninvolved by DIP was present in the specimen, it showed an absence of centrilobular emphysema. Focal mild intra-alveolar organization common. Interesting aside – EM studies have shown intercellular connections between macrophages in DIP (unpublished personal communication).

Clinical course: 18/19 patients (95%) improved under steroid pulse and/or oral therapy. Sixteen subjects (80%) are alive, three died of other diseases and one died of DIP 74 months after the diagnosis. Percent vital capacity increased significantly and new thin-walled cysts appeared in one case.

Conclusions: BAL eosinophilia, lobular distribution and architectural destruction with cyst formation are characteristic features of DIP.

Limitations: Retrospective and selective study. No statistical significance reported on the BAL results – data for eosinophils appears skewed (mean >> than median).

Take home message: Confirmed that **BAL eosinophilia is a characteristic feature of DIP**, sometimes to levels typical of chronic eosinophilic pneumonia. Tissue eosinophilia however is mild. **Variation in severity from lobule to lobule** an important diagnostic feature. Focal mild intra-alveolar organization is common and doesn’t preclude diagnosis.

<table>
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<tr>
<th>Border of lesion (abrupt/gradual/not estimated, abnormal %)</th>
<th>5/7/8, 25%</th>
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<tr>
<td>Interlobular difference of interstitial fibrosis (+/-, abnormal %)</td>
<td>7/13, 65%</td>
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<tr>
<td>Lobular based distribution</td>
<td>14 (70%)</td>
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<tr>
<td>Predominant area of interstitial fibrosis (PL, CL, PP)</td>
<td>17/1/2</td>
</tr>
<tr>
<td>Tissue destruction/emphysema (no/mild/moderate, abnormal %)</td>
<td>6/10/4, 70%</td>
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<tr>
<td>Cyst formation (no/mild/moderate, abnormal %)</td>
<td>9/10/1, 95%</td>
</tr>
<tr>
<td>Location of cyst (panlobular/centrilobular), n = 11</td>
<td>6/5</td>
</tr>
<tr>
<td>Intra-alveolar organization and incorporation (no/mild/moderate, abnormal %)</td>
<td>2/16/2, 90%</td>
</tr>
<tr>
<td>Tissue eosinophils (no/mild/moderate, abnormal %)</td>
<td>1/19/0, 95%</td>
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PL, Panlobular; CL, centrilobular; PP, peribronchovascular predominance.

**Rationale:** Sarcoïdosis is a markedly heterogeneous disease. Scadding classification based on radiologic criteria widely used, but is insufficient for clinical decision making. Therefore, biomarkers and genetic markers that predict outcome are urgently needed

**Objectives:** To obtain a classification system based on clinical criteria to evaluate biomarker and genetic markers.

**Methods:** Classification of various disease courses (sarcoid clinical activity classification [SCAC]) based on clinical criteria: (1) whether the disease was acute or nonacute in onset, (2) whether treatment was required, and (3) whether there was need for long-term treatment. Produced 6 clinical classes as opposed to the 5 categories produced by radiologic criteria.

**Results:** Evaluated 225 patients with sarcoidosis, applying both classification protocols retrospectively. The classes of patients with chronic disease differed significantly regarding pulmonary function test parameters and bronchoalveolar lavage fluid cell composition. Concentrations of soluble IL-2 receptor and neopterin were increased in patients with acute disease who required long-term treatment and in those with nonacute disease who needed long-term treatment. In contrast to the clinical classification system, the system based on radiologic criteria separated the patients with the need for long-term therapy insufficiently, but identified patients with advanced fibrotic remodeling.

**Authors Conclusions:** The described SCAC protocol is practicable and gives additional information not yet acquired by radiologic typing and seems suitable for studies evaluating genetic influence and biomarkers.

**Limitations of Study:** Retrospective. Highly selected group. ‘Pulmonary’ perspective – only sampled BAL – histology might have been useful. Very few numbers classified as CXR type 0 (n = 9), and type IV (n = 4). Classification based on response to treatment, therefore not practically useful at this stage. Poor correlation with CXR (Scadding) classification, therefore confusing. Both classifications (‘clinical’ and CXR types) are related to progressively decreasing FEV1, although there is poor correlation between the two classifications. Already known that patients who present acutely have a better prognosis.

**Take Home Message:** A clinical classification based on onset (acute/subacute/chronic) and need for immunosuppressive treatment might identify phenotypes that can be later identified by genotypes and gives additional information over that given by radiological typing.
**Rationale and Objectives:** Patients with a clinicopathological diagnosis of idiopathic pulmonary fibrosis (IPF) have a range of findings on HRCT from typical findings of usual interstitial pneumonia (UIP) to nonspecific interstitial pneumonia (NSIP). Previous paper (Flaherty et al. Thorax 2003; 58:143) reported that the prognosis of cases that were diagnosed as UIP based on both CT and histologic findings was worse than in cases with a histologic diagnosis of UIP but without CT features of UIP. The authors wanted to revisit HRCT findings of IPF and assess correlation with prognosis.

**Methods:** Three institutions identified 154 patients with clinical and histologic criteria for IPF diagnosis recommended by the ATS/ERS consensus classification of the IIPs. All biopsies reviewed by a very experienced pathologist and only those cases diagnosed as UIP on the basis of the new recommendations included. Finally, 98 patients who had a confident histologic diagnosis of UIP made by two independent lung pathologists and who had a clinical diagnosis of IPF were included in the study. Two observers evaluated the CT findings independently and classified each case into either: (1) definite UIP, (2) consistent with UIP, or (3) suggestive of alternative diagnosis. Chest radiologists were divided into two groups of two radiologists each. In each group, the images were assessed independently, and the findings were agreed upon by consensus between the two radiologists. All radiologists were informed about pathological and clinical UIP diagnosis. The median follow-up periods were 63 months. Forty-six patients died and 10 were lost to follow-up. The correlation between the CT categories and mortality was evaluated using the Kaplan-Meier method and the log-rank test, as well as Cox proportional hazards regression models.

**Results:** Interobserver agreement was poor to moderate for the presence of architectural distortion and the predominant distribution and poor for the presence of nodules. The interobserver agreement of CT diagnosis into consistent with UIP (definite or probable) or suggestive of alternate diagnosis (suggestive of NSIP or indeterminate) was moderate.

- Definite UIP – 33/98: mean survival 45.7 mths
- Consistent with UIP – 29/98: mean survival 57.9 mths
- Alternative diagnosis – 29/98: mean survival 76.9 mths

No significant difference in survival among the three categories. Traction bronchiectasis and fibrosis scores were significant predictors of outcome.

**Authors Conclusions:** In patients with clinicopathological diagnosis of IPF, the pattern of abnormality on HRCT (typical of UIP or alternative) did not influence prognosis. Prognosis was influenced by traction bronchiectasis and fibrosis scores.
**Limitations of study:** Retrospective. Three different sites with heterogeneous treatment. No correlation of findings with physiologic parameters. Second pathologist did not diagnose independent of diagnosis by first pathologist. Study biased towards patients with atypical clinical and/or CT findings since those with typical findings wouldn’t have had biopsies done otherwise. Even though it is accepted that typical IPF can have atypical CT findings, it is likely that radiologists would have been biased by knowing that the histology was typical for UIP. Failure to find a significant difference may be due to small sample size and type II error.

**Take-home message:** Essentially a radiologic study of HRCT done in patients with a confident diagnosis of IPF on clinical and pathologic criteria. Although could not confirm the previous paper which concluded that atypical CT findings in patients with IPF are predictive of a better prognosis, the study was inconclusive and unable to refute Flaherty’s paper. Further studies need to be done with greater power and designed free of bias.

Striking finding was that CT varied markedly despite very rigid histopathologic criteria. Therefore, indicates that a surgical lung biopsy is critical in patients without definite HRCT appearance of UIP even when NSIP diagnosis is confidently made on HRCT.

The pathogenic importance of smoking status in IPF is uncertain. In theory, increased oxidative stress in current and former smokers might promote disease progression. However, better survival has been reported for current smokers with IPF, although this might reflect less severe disease at presentation (a "healthy smoker effect"). Need to rigorously adjust for baseline disease severity in the survival analyses. Routine indices, (DLco and FVC) are influenced by coexistent smoking-related damage. Composite physiologic index (CPI) adjusts for confounding functional effects of concurrent emphysema. A total of 249 patients with IPF were retrospectively studied (current smokers, n = 20; former smokers, n = 166; never-smokers, n = 63). Survival was evaluated against smoking status, using proportional hazards analysis, adjusting for sex, age, disease severity (extent of the disease on HRCT, composite physiologic index [CPI], percentage predicted diffusing capacity for carbon monoxide in separate models), and the degree of honeycombing.

Results: Current smokers had milder disease than did former smokers, with lower CPI scores, less extensive disease on HRCT, and higher unadjusted survival. However, survival did not differ between current and former smokers after adjustment for CPI levels. By contrast, the increase in survival seen in nonsmokers than in former smokers was amplified by adjustment for CPI levels.

Conclusions: In IPF, survival and severity-adjusted survival are higher in nonsmokers than in former smokers or the combined group of former and current smokers. By contrast, a better outcome in current smokers, compared with former smokers, reflects less severe disease at presentation and may represent a healthy smoker effect.
Rationale: Lung and pleura are the commonest metastatic sites for breast carcinoma after bone. Important to distinguish from lung primary as treatment modalities are different. ER and PR only positive in a proportion of breast carcinomas (24-63% and 9-37% respectively). Mammoglobin reported as positive in primary breast carcinoma 48-71% (the higher % rates used non-commercial antibody). Lung cancers – ER and PR positive in 0-96.7% and 0-46.5% respectively! Gross cystic disease fluid protein 15 (GCDFP-15) reported as positive in 0-3.3% of lung tumors. [Surprisingly, mammoglobin reported as positive in 6/23 of pulmonary adenocarcinomas in the package insert for the DAKO antibody, M3625]. [Mammoglobin is expressed in up to 40% endometrial adenocarcinomas, in skin adnexal tumors, salivary gland tumors and a few melanomas].

Objective: To elucidate the utility of mammoglobin and GCDFP-15 in distinguishing various primary lung and pleural tumors from breast carcinoma metastasizing to the lung.

Methods: Commercial antibodies (mammoglobin, DAKO and GCDFP-15, Signet) used and labeled with EnVision+/HRP system (DAKO). 20 cases of breast carcinoma metastatic to the lung and 263 tumors of nonbreast origin located in the lung and pleura were analyzed (Table 1). Grading the intensity of immunostaining was performed using a sliding scale of 0 to 3 according to the percentage of reactive cells (0 =<1%; 1+ = 1%–10% (should this be 2- 25%? 11-25%?); 2+ = 26%–50%; 3+ = 51%–100%).

Results:

<table>
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<tr>
<th>Table 1. Immunoreactivity of Mammoglobin</th>
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<tr>
<td><strong>No. of Cases</strong></td>
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<tr>
<td><strong>Breast carcinoma, metastases to lung</strong></td>
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<tr>
<td><strong>Primary lung carcinoma</strong></td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>Pleomorphic carcinoma</td>
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<td>Carcinoïd tumor</td>
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<td>Large-cell neuroendocrine carcinoma</td>
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<td>Small-cell carcinoma</td>
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<td>Adenoid cystic carcinoma</td>
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<td>Mucoepidermoid carcinoma</td>
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<td>Malignant mesothelioma</td>
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<th>Table 2. Immunoreactivity of Gross Cystic Disease Fluid Protein 15</th>
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<td><strong>No. of Cases</strong></td>
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<tr>
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Of the 20 cases of breast carcinoma metastatic to the lung, 10 (50.0%) were immunoreactive for mammaglobin and 9 (45.0%) for GCDFP-15. “The area immunopositive for mammaglobin showed more diffuse staining than the area immunopositive for GCDFP-15” – don’t agree with this. All primary lung adenocarcinomas negative for mammaglobin (including cribriform and/or acinar types, of which there were 20); GCDFP-15 positive in 15% (all cribriform and/or acinar types). Both markers negative in solid types of adenocarcinoma (20 cases). Both equally positive in carcinoid (5.2%). Quite a high (40%) positive rate for GCDF-15 in mucoepidermoid carcinoma. Most squamous cell carcinomas and all malignant mesotheliomas were negative for both markers. The specificity of mammaglobin for breast carcinoma metastatic to the lung was superior (98.9%) to that of GCDFP-15 (91.8%).

Authors Conclusions: The sensitivity of mammaglobin is equal or superior to that of GCDFP-15 for investigation of breast carcinoma. (Immunopositivity for mammaglobin is more diffuse than that for GCDFP-15 – too few numbers). In terms of practical diagnosis, mammaglobin immunohistochemistry can serve as a differential marker of breast carcinoma and should be added to the immunohistochemical panel.

Limitations of study: Is it reasonable to include > 1% staining as positive? The authors describe the lung tumors as ‘nonbreast’ – was there some worry that these may be tumors metastatic from other organs? What was the level of confidence that the tumors were all primary to the lung? No breast carcinomas metastatic to the pleura were included – would be useful as differential diagnosis of malignant pleural effusions difficult. (Cancer. 2004 102:368 reported mammoglobin pos in 55% pleural effusions secondary to breast ca). No description of the primary type of breast carcinoma or the hormone receptor status. Would have been interesting to have compared the immunostaining of the primary and secondary breast carcinomas. Previous studied showed that concordance rate of mammaglobin expression between the primary site and lymph node mets was 93% - can’t directly extrapolate that to lung mets). No analysis of whether the sensitivity of mammaglobin was statistically better than GCDFP-15. Cannot describe the staining of mammaglobin as being more diffuse than GCDFP-15. Not clear that the use of both markers is much of an advantage as stated by the authors.

Take home message: Mammoglobin or GCDFP-15 are negative in breast carcinoma metastasis to the lung in about 50% of cases but if positive, they have a specificity of > 90%, with mammaglobin appearing to be the most specific marker when an adenocarcinoma is being considered, especially if has acinar and/or cribriform pattern (0/100 lung adenocarcinomas positive for mammaglobin).
ARTICLES FOR NOTATION

Techniques:


Dithiothreitol (DTT) is commonly used to liquefy induced sputum samples before assessment of cytology, denatures proteins by disrupting disulfide bonds. The measurement of chemokines and cytokines in sputum is an attractive, non-invasive method to investigate and followup patients with pulmonary disease. However, the denaturation of proteins, making them difficult to detect by ELISA, is a major drawback. Proteases in sputum have also been shown to reduced levels of detection of various proteins. The authors have done an enormous amount of work in the past few years to solve these problems, and have come up a method to improve recovery of proteins. Essentially it involves optimized dialysis of sputum to remove DTT and restore immunoreactivity. A cocktail of protease inhibitors was also used. Optimized dialysis permitted recovery of chemokines to 96 +/- 4% and cytokines to 91 +/- 6%. The authors also demonstrated that, in addition to increasing recovery of chemokine/cytokines and the repeatability of their measurements, they were able to detect significant differences in levels of these proteins in subjects with severe asthma. The detection of elevated levels of particular sputum chemokines and cytokines in individual patients may provide a rationale for specific therapies e.g. therapy directed towards TNF-alpha. The only drawback of the method is that it seems quite cumbersome and time-consuming and is unlikely to be readily adopted except by specialized laboratories. Despite this, it is a great advance as the authors have greatly extended the utility of sputum samples.


Exhaled breath condensate may be an attractive noninvasive alternative to bronchoscopy, bronchoalveolar lavage and induced sputum for diagnosis and monitoring of pulmonary disease. Authors have previously shown that microsatellite alterations are detectable in exhaled breath condensate and are more frequent in patients with NSCLC (Am J Respir Crit Care Med 2005;172:738). In this study, subjects undergoing histologic diagnosis for clinical suspicion of lung cancer –
- 41 NSCLC
- 18 nonneoplastic diseases
All subjects underwent allelotyping on DNA from whole blood, exhaled breath condensate, and lung tissue removed for histologic diagnosis by analyzing a panel of five microsatellites located in chromosomal region 3p.
The authors found that microsatellite alterations were more prevalent in heavy smokers compared with other smokers, although this analysis may be confounded by disease and by classification bias. Microsatellite alterations in DNA from tumor tissues and exhaled breath condensate of each patient presented an overlapping profile of loss of heterozygosity and microsatellite instability (Table 3). Not known what the source of the DNA in exhaled breath condensate, and it may be that nonmalignant lung tissue also harbours these abnormalities. Exhaled breath condensate analysis could potentially be used for early diagnosis of lung cancer but much work needs to be done before it is clinically useful.

Hoffmann et al. Human skin keratins are the major proteins in exhaled breath condensate. Eur Respir J. 2008;31:380-4.

Saliva, ambient air condensate (AAC) and exhaled breath condensate were collected from normal human volunteers with or without a filter to remove particles from air. Samples were freeze-dried and analysed by SDS-PAGE. Three major bands were seen in exhaled breath condensate and AAC, and were identified by mass spectrometry and found that CK1, CK2 and CK10 (keratinizing epidermis proteins, continually shed into ambient air and inhaled into respiratory tract) were the major protein detected and derived from ambient air and not the respiratory tract. In the light of these studies, it is important to determine whether cytokines measured in exhaled breath condensate derive from the lung or whether they, like keratin, are debris from ambient air.


Molecular testing in pathology emerged shortly after polymerase chain reaction became a standard molecular biology assay. The field has evolved into "molecular diagnostics," which encompasses testing in almost every area of anatomic pathology. Molecular testing is now even making its way definitively into both surgical pathology and cytopathology, although molecular anatomic pathology is still young with few standard tissue-based molecular assays. This review focuses on basic molecular pathology concepts, with particular emphasis on the challenge of tissue-based testing in anatomic pathology.


Molecular testing in anatomic pathology is going to become more and more important during the next decade as we develop assays that can aid in diagnosis, prognosis, and predicting response to therapy. The anatomic pathologist needs to be familiar with the different assays available but also needs to be able to discern which are going to become standard of care and which will not. Three different types of tumors are reviewed: thyroid cancer, oligodendroglioma, and lung carcinoma. Molecular assays that are currently in use or on the near horizon, including translocation analyses for RET-PTC and
PPARgamma-PAX8, point mutation analysis for BRAF and epidermal growth factor receptor, and genetic loss for 1p and 19q, are discussed.


Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) is rapidly becoming a basic method in lung cancer research. Analysis of transcriptional activity of tumor cells or detection of tumor markers by this technique has the potential to change lung cancer diagnosis and treatment. Quantitative RT-PCR is characterized by unparalleled sensitivity and specificity, with very reliable reproducibility. Its prime advantage for gene expression analysis is its broad dynamic range of 10(7)-fold. Moreover, it is cost-effective, feasible in every day laboratory routine and efficient in terms of biological material consumption. Still, there are a number of methodological aspects that need to be carefully considered before it can sensibly be implemented into clinical practice. Three major technical issues: the choice of chemistries, gene expression data normalization and statistical processing of the results are specifically highlighted in this review. Clinical applications of qRT-PCR are also thoroughly discussed, namely, detection and staging of lung cancer and construction and validation of prognostic and predictive gene expression signatures.

Neoplasia


Neural (N)-cadherin belongs to a group of transmembrane molecules with a crucial role in tissue morphogenesis and maintenance of an epithelioid phenotype. Increased N-cadherin expression is implicated in tumour progression and dedifferentiation. Pulmonary neuroendocrine tumours encompass a broad range of phenotypically diverse neoplasms with a spectrum of clinical outcomes: low-grade typical carcinoid (TC), the intermediate-grade atypical carcinoid (AC) and the extremely aggressive small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNC). Prognosis is related to degree of differentiation, but, although the majority of TC behave non-aggressively, metastatic spread has been documented in 5–10% of cases. SCLC is the only one treated by chemotherapy and not surgical resection. Identification of a marker to separate high-grade from low-grade lesions, or SCLC from non-small cell lung carcinoma, would be useful and it was hypothesized that N-cadherin might be more strongly expressed in more aggressive lesions.

N-cadherin expression was demonstrated mainly in neuroendocrine lesions. Surprisingly, the more differentiated lesions with a lower malignant potential had the highest expression of N-cadherin: all cases of benign neuroendocrine hyperplasia expressed N-cadherin, >95% TC, AC >80%, two-thirds of SCLC and one-third of LCNC, with a
significantly lower intensity of reactivity than for TC or AC. Increased N-cadherin expression in typical carcinoids was associated with negative lymph node status (P < 0.001). Authors propose that this marker be used similarly to chromogranin and CD56 to identify TC and AC.

**Interstitial Lung Disease:**

**Barrera et al. Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med 2008;177:44-55.**

Hypersensitivity pneumonitis (HP) exhibits a diverse outcome. Patients with acute/subacute HP usually improve, whereas patients with chronic disease often progress to fibrosis. The mechanisms underlying this difference are unknown and may be related to the types of T cell subsets present. Controversial whether HP is a ‘Th1’ type disease (T cells secrete IFN-gamma and TNF-alpha, as opposed to ‘Th2’ cells which secrete IL-4 and IL-13). Th2 activity is believed to be related to the pathogenesis of fibrosis. T cells were obtained by bronchoalveolar lavage from 25 patients with subacute HP, 30 patients with chronic HP, and 8 control subjects. Patients were defined clinically +/- tissue diagnosis: 15/25 patients with subacute HP had biopsy (inflammatory infiltrates without fibrosis) and 22/30 patients with chronic HP (>20% fibrosis). Concluded that patients with chronic HP lose effector T-cell function and exhibit skewing toward Th2 activity, which may be implicated in the fibrotic response that characterizes this clinical form.

**Mylärniemi et al. Gremlin-mediated decrease in bone morphogenetic protein signaling promotes pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:321-9.**

Members of the transforming growth factor (TGF)-beta superfamily, including TGF-betas and bone morphogenetic proteins (BMPs), are essential for the maintenance of tissue homeostasis and regeneration after injury. The authors previously showed that a BMP antagonist, gremlin, is highly up-regulated in IPF (Koli et al. Am J Pathol 2006; 169:61). They took this observation to a mouse model of asbestos-induced fibrosis and administered BMP-7 to these mice. Gene expression of Gremlin was up-regulated in the asbestos-exposed mouse lungs, but there was down-regulation of BMP signaling. Analyses of cultured human bronchial epithelial cells indicated that asbestos-induced gremlin expression could be prevented by inhibitors of the TGF-beta receptor and also by inhibitors of the mitogen-activated protein kinase pathways. BMP-7 treatment significantly reduced fibrosis in the asbestos-treated mice. Rescue of BMP signaling activity may represent a potential beneficial strategy for treating human pulmonary fibrosis.

Granulomatous inflammation in lung biopsies is a relatively non-specific finding that can occur in a range of inflammatory and neoplastic conditions. This review focuses on the patterns of granulomatous inflammation that can cause diffuse lung disease, highlighting histopathological features helpful in differential diagnosis.


In patients with interstitial lung disease (ILD), the diagnosis of IPF is usually made after excluding, among other conditions, connective tissue diseases (CTDs). Although in most patients with a CTD and respiratory symptoms, the systemic nature of the disease is obvious, the ILD-related manifestations in CTDs may often dominate the clinical picture or precede systemic findings and thus mimic IPF. With the exception of systemic lupus erythematosus, all CTDs may imitate chronic IPF. Clues to an underlying CTD may be entirely absent or include subtle findings from various systems, including skin, vascular and musculoskeletal system or internal organs. Since nonspecific interstitial pneumonia is a relatively frequent histological pattern in CTDs, biopsy reports of nonspecific interstitial pneumonia should also prompt a search for an underlying CTD. Ultimately, diagnosis of a CTD requires confirmation with immunological testing; interpretation of the various laboratory tests should always be carried out in conjunction with clinical findings. The present article reviews specific clinical aspects of connective tissue disease-related interstitial lung disease that may help differentiate it from idiopathic interstitial pneumonia, especially when interstitial lung disease is the predominant or sole manifestation of an occult connective tissue disease.


A total of 1,027 patients were enrolled from a cluster encompassing 79.4% of the entire Japanese population. The study participants consisted of 364 males and 663 females, providing an average incidence rate of 1.01 per 100,000 inhabitants (0.73 for males and 1.28 for females). The male incidence rates peaked in the 20-34-yr-old group. A second peak for 50-60-yr-old females showed a higher incidence than the first younger peak. Patients with abnormalities in eyes, skin and cardiac laboratory findings accounted for 54.8, 35.4 and 23.0% of cases, respectively. The female/male incidence ratio was increased, and the frequency of eye and skin involvement and cardiac abnormality was higher than in previous surveys conducted in Japan. In conclusion, the data obtained in the present study differ from those of other countries and showed changes in sarcoidosis clinical phenotypes compared with previous studies in Japan.
Airway Inflammation: Chronic Obstructive Pulmonary Disease/Asthma


The authors compared dendritic cell (DC) numbers in endobronchial biopsies from 20 patients with moderate-severe COPD (15 current smokers, 5 ex-smokers), 11 non-smokers with asthma and 11 non-smoker healthy controls. Transmission electron microscopy (TEM) was used to identify the total population of DCs by their ultrastructure: (1) the presence of pseudopodia; (2) nuclear indentation with peripheral distribution of heterochromatin; and (3) abundance of cytoplasm which was electronlucent and containing numerous micropinocytic vesicles, profiles of endoplasmic reticulum and free ribosomes. All DC’s were described as being of the myeloid subtype, no plasmacytoid DCs with detected. Novel method of enumerating DC’s and theoretically includes all DCs, an advantage over immunohistochemical methods [but a disadvantage in that different subsets not discriminated].

![Graphs showing A) number of dendritic cells (DCs) per mm² of bronchial epithelium; B) number of DCs per mm² of bronchial subepithelium; and C) number of DCs per mm of bronchial epithelium of the four groups studied (lines indicate median value). COPD-Ex, ex-smoker with chronic obstructive pulmonary disease; COPD-C, current smoker with chronic obstructive pulmonary disease. Significant differences determined by the Mann-Whitney U test.](image)

In COPD, bronchial mucosal DC numbers were lower in current smokers while, in those who quit, numbers were similar to non-smoking subjects with asthma and non-smoking healthy controls. Speculate that smoke-induced reduction of the overall number of DCs in COPD (and of their mature subset in asthma, together with the findings of reduced DC function reported by others), would alter normal immunity and may facilitate infection by virus and lead to increased exacerbation frequency.
Infection


Pneumocystis pneumonia (PCP) is conventionally diagnosed by identifying *Pneumocystis jirovecii* in lower respiratory tract samples using cytochemical stains. A number of studies have been published utilizing molecular diagnostic methods which are potentially more sensitive. The authors used an optimised real-time PCR with primers designed to hybridise with the *P. jirovecii* HSP70 gene to quantify *P. jirovecii* DNA in BAL fluid in patients with and without PCP diagnosed by cytological methods. They compared this assay with conventional PCR targeting the *P. jirovecii* mitochondrial large subunit rRNA gene sequence (mt LSU rRNA). The authors method showed a clinical sensitivity of 98% and specificity of 96% for diagnosis of PCP. By contrast, clinical sensitivity of mt LSU rRNA PCR was 97% and specificity was 68%. In addition, quantification of *P. jirovecii* DNA by real-time PCR may also discriminate between colonisation with *P. jirovecii* and infection. Quantification in a sample such as BAL which has variable dilution is difficult, but the authors suggest that normalizing to genomic DNA or by including internal amplification controls might get around this. A large prospective translational study is required to define the utility of this diagnostic approach in a routine clinical setting.


The authors describe the epidemiology of *Mycobacterium tuberculosis* infection in the United States in the noninstitutionalized civilian population participating in the 1971-1972 and 1999-2000 National Health and Nutrition Examination Surveys. Participants were tuberculin skin tested and the epidemiology of TB infection was compared across surveys. In 1999-2000, decline in the relative burden of infection among 25-74 year olds were greater in the US-born population (12.6 to 2.5%) compared with the foreign-born population (35.9 to 21.3%). Although the US has experienced a substantial decline in the burden of TB infection since the early 1970s, the prevalence of infection in the foreign-born population is over eight times greater than that observed in the US-born population.


The authors aimed to estimate the prevalence of latent tuberculosis infection (LTBI) in the U.S. population in 1999-2000 as part of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the civilian, noninstitutionalized U.S. population. LTBI was defined as a TST measurement of >/=10 mm. Among 25-74-year-olds estimated LTBI prevalence was 4.2% overall; higher prevalences were seen in the foreign born (18.7%), non-Hispanic blacks/African
Americans (7.0%), Mexican Americans (9.4%), and individuals living in poverty (6.1%). A total of 63% of LTBI was among the foreign born. Among the U.S. born, after adjusting for confounding factors, LTBI was associated with non-Hispanic African-American race/ethnicity, Mexican American ethnicity, and poverty. A total of 25.5% of persons with LTBI had been previously diagnosed as having LTBI or TB, and only 13.2% had been prescribed treatment.


A very good review and update on what is known about the basic mechanisms of LRTI.

Pulmonary Vascular Disease:


The aim of the present study was to describe a large cohort of fenfluramine-associated pulmonary arterial hypertension (fen-PAH) and its possible prognostic markers. The records of all patients with a diagnosis of fen-PAH evaluated at the present authors' centre from 1986-2004 were retrospectively studied. The median duration of fenfluramine exposure was 6 months, with a median of 4.5 yrs between exposure and onset of symptoms. 22.5% of 40 patients evaluated were positive for the presence of germline bone morphogenetic protein receptor (BMPR) type 2 mutations, (a very similar incidence to that observed in sporadic IPAH). In these patients, the duration of exposure to fenfluramine was significantly lower than in patients without mutation. The median survival was 6.4 yrs, without significant difference between fen-PAH and a control group of idiopathic and familial pulmonary arterial hypertension patients. Duration of fenfluramine exposure showed no relation to survival. Therefore, the authors concluded that fenfluramine exposure characterises a potent trigger for pulmonary arterial hypertension without influencing its clinical course.

The accompanying editorial describes some of the complex mechanisms shared between fen-PAH and IPAH - increased plasma 5-hydroxytryptamine, abnormal function of the 5-hydroxytryptamine transporter and a decrease in K+ channel function/expression. New drugs should be screened for these characteristics. ‘We are beginning to understand the hieroglyphics on our Rosetta stone’.