224a Pulmonary Pathology: New and Evolving Concepts, Diagnostic Dilemmas and Controversies (Part 1- Cases)

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2011 Annual Meeting – Las Vegas, NV

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224a Pulmonary Pathology: New and Evolving Concepts, Diagnostic Dilemmas and Controversies (Part 1-Cases)

This session consists of a series of didactic case presentations as a means to discuss new and evolving concepts, diagnostic dilemmas and areas of controversy in Pulmonary Pathology. Specific topics addressed include 1) the current role of molecular testing in non small cell lung cancer (NSCLC) including EGFR, EML4-ALK and the determination of histologic phenotype, 2) the new classification of pulmonary adenocarcinoma including the proposed reclassification of bronchioloalveolar cell carcinoma as adenocarcinoma in situ, 3) the distinction of fibrosing nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) patterns and their mimics, 4) the pathologic spectrum of subacute and chronic hypersensitivity pneumonitis, 5) the classification of pulmonary neuroendocrine neoplasia, 6) selected topics in the classification of pulmonary lymphoproliferative disorders including lymphomatoid granulomatosis, low grade BALT lymphoma and pulmonary involvement by IgG4 related systemic disease. The presentation is designed to enhance participants' diagnostic skill in the diagnosis of covered entities, guide participants in the role and selection of appropriate molecular tests, and enhance overall medical knowledge in these areas.

- Following this session, participants will be able to recommend the use of specific ancillary molecular tests in helping to predict the response of non small cell lung carcinoma to new therapeutic agents such as gefitinib, erlotinib, and others. They will be able to communicate the rational behind their use.
- Following this session, participants, will be able to diagnose non mucinous bronchioloalveolar cell carcinoma and interpret the rationale behind its proposed reclassification as adenocarcinoma in situ. Participants will be able to detect microinvasion and evaluate its significance.
- Following this session, participants will be able to recognize key diagnostic features helpful in the distinction of a UIP pattern from fibrosing NSIP and chronic hypersensitivity pneumonitis. They will be able to better integrate clinical and radiologic correlation in arriving at the best overall interpretation.

FACULTY:

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Practicing Pathologists
Surgical Pathology
Surgical Pathology (Derm, Gyn, Etc.)

2.0 CME/CMLE Credits

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Hypersensitivity Pneumonitis

Pulmonary Pathology – New and evolving concepts, diagnostic dilemmas and controversies.

2011 ASCP Annual Meeting – Las Vegas, NV, USA

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Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is an interstitial lung disease which results from inhalation and sensitization to a wide variety of extraneous organic dusts. Clinically, these diseases have been named according to the offending agent. Thus “farmer’s lung” is the term applied to farmer’s who develop a hypersensitivity pneumonitis from exposure and sensitization to moldy hay (Saccharopolyspora rectivirgula), bagassosis from moldy sugar cane (Thermoactinomyces saccharii), maple bark strippers disease from moldy maple bark (Cryptostroma corticale); and such animal associated entities as bird fancier’s lung from inhalation of proteins from pigeon droppings. The number of known causes of HP continues to grow. For example, mycobacterium avium complex has been implicated as a cause of HP in patients using hot tubs with water contaminated with the organism. Table 1 lists examples of agents known to cause hypersensitivity pneumonitis and their associated diseases.

Clinical Features:

Clinically, hypersensitivity pneumonitis may present either acutely, subacutely or chronically. In the acute presentation, individuals develop fever, chills, malaise, dry cough and dyspnea from 4 to 6 hours after exposure. These symptoms slowly resolve over the next 12 hours if the offending antigen is avoided. The acute form is rarely biopsied.

In the subacute presentation, individuals have gradual onset of dyspnea, dry cough, fatigue, weight loss and malaise over days or weeks. Often the patients experience repeated acute episodes sometimes leading to hospitalization.

An insidious or chronic form results from continued usually low-level antigen exposure occurs. A patient with chronic HP may not remember of experience any acute episodes. Disabling and frequently irreversible respiratory findings, i.e., pulmonary fibrosis, are characteristic. In many cases of chronic HP the inciting antigen may be very difficult to detect and may never be identified.

Diagnosis at the subacute or chronic stages may require lung biopsy. Early diagnosis is critical since irreversible or progressive disease can occur.

Laboratory Features:

The most helpful adjunctive laboratory test is the identification of antibodies to the inciting antigen by ELISA or agar gel diffusion techniques. Other findings include a
positive skin test. Aerosol challenge has also been used and is considered the “gold standard”, but may evoke severe reactions.\textsuperscript{12-16}

**Radiologic Features:**

In subacute HP, chest X-ray shows a bilateral reticulonodular interstitial infiltrate.\textsuperscript{17} High resolution CT scan shows a variable combination of ground glass opacities, centrilobular nodules, air trapping (mosaic pattern) and variable degrees of mild fibrosis.\textsuperscript{18-20} In chronic HP, high resolution CT scan shows greater fibrosis with peripheral honeycombing in some patients. In approximately half of patients there are associated ground glass opacities. In 25\% of patients with chronic hypersensitivity pneumonitis, the features are indistinguishable from idiopathic pulmonary fibrosis.\textsuperscript{21}

**Histologic Features:**

**Acute phase:**

Although biopsies are seldom necessary in the acute phase they may rarely be performed in cases in which the clinical symptoms are severe and the underlying diagnosis is not clear. Hariri et al reported a series of 8 patients, 5 of whom had clinically confirmed hypersensitivity pneumonitis with rapid onset of symptoms and 3 of whom had acute symptom exacerbation on a clinical background of subacute or chronic hypersensitivity pneumonitis. Biopsies in these cases showed typical features of subacute hypersensitivity pneumonitis with additional findings of significant intraalveolar fibrin deposition and interstitial neutrophilic infiltrates. In two cases, the extent of intraalveolar fibrin deposition was so extensive as to resemble acute fibrinous and organizing pneumonia.\textsuperscript{22} Analysis of BAL fluid has shown a mixture of neutrophils, mast cells, lymphocytes and monocytes.\textsuperscript{9,23}

**Subacute phase**

Pathologic studies of hypersensitivity pneumonitis were initially based on patients in the subacute phase. Biopsies from these patients classically show a histologic triad of a chronic interstitial pneumonitis with bronchiolar accentuation, small poorly formed interstitial granulomas and foci of organizing connective tissue within bronchioles and / or airspaces (foci of organizing pneumonia (OP) (table 2a).\textsuperscript{13,16,17,24} Other less specific pathologic features which are often present include foci of foamy macrophages within alveolar airspaces (foci of obstructive pneumonia), cholesterol clefts and calcium deposits within the giant cells and (rarely) foci of neutrophils.\textsuperscript{17,24}
While the combination of a chronic interstitial pneumonitis, granulomas and foci of organizing pneumonia are typical and virtually diagnostic of hypersensitivity pneumonitis, they are not always present. For example, in Kawanami’s study, granulomas were only identified in 2/3 of cases of hypersensitivity pneumonitis. {Kawanami, 1983 #809}

More recent studies have extended these observations and shown that the histologic features vary according to the type of antigen exposure. In an epidemiologic survey of 36 patients with hypersensitivity pneumonitis in Japan, Yoshizawa, et al found that granulomas were identified in only 16.7% of patients with bird fancier’s lung, whereas they were much more prevalent (44.4% and 60.0%, respectively) in summer type and isocyanate associated hypersensitivity pneumonitis. {Khoor, 2001 #951; Barrios, 2008 #2022} Likewise, exuberant non-necrotizing, bronchiolocentric, granulomatous inflammation is characteristic of so called “hot tub lung”, thought to be a hypersensitivity reaction to inhalation of mycobacterium avium-intracellular complex from contaminated bathing waters. In Churg’s study, 19 of 24 patients (79%) with subacute hypersensitivity pneumonitis had a pattern of bronchiolocentric interstitial pneumonia. The other five patients (21%) had a pattern of cellular NSIP. As in other studies, granulomas were present in a majority 19 of 25 (79%) but not all of biopsies. {Khoor, 2001 #951; Barrios, 2008 #2022} Thus, in the appropriate clinical setting, the possibility of hypersensitivity pneumonitis should be entertained in biopsies which show only chronic interstitial pneumonia with bronchiolar accentuation and small non necrotizing granulomas (but no foci of BOOP), biopsies which show only a bronchiolocentric chronic interstitial pneumonitis (NSIP pattern) or an OP pattern, or biopsies which show exuberant fairly well formed granulomas.

Chronic phase

In patients with chronic stages of hypersensitivity pneumonitis, fibrosis may be the dominant feature and more classic findings may be only focal or even absent altogether. {Churg, 2001 #951; Barrios, 2008 #2022} In Churg’s most recent study, he found that 18 of 25 (72%) of lung biopsies from patients with chronic hypersensitivity pneumonitis showed a pattern resembling UIP, whereas 4 cases (16%) resembled fibrotic NSIP and 3 cases (12%) had only peribronchiolar fibrosis. In most of the biopsies resembling UIP, there was a greater degree of peribronchiolar fibrosis than typical of IPF. (table 2b). In half the cases (13 of 25), these patterns lacked more classic histologic changes of hypersensitivity pneumonitis (areas of subacute hypersensitivity pneumonitis). In these cases, the only clue to hypersensitivity pneumonitis was rare ill defined granulomas, multinucleated giant cells or sometimes only Schaumann bodies. These features could be found in most (22 of 25 or 88%) but not all biopsies. {Churg, 2001 #951; Barrios, 2008 #2022} Based on these and other
The presence and type of pattern of fibrosis has an impact on prognosis. In a study of 26 patients with chronic bird fancier’s lung, patients with fibrotic NSIP or UIP patterns had a much worse prognosis than those with an OP or cellular NSIP pattern (30% - 40% vs. 100% survival at 5 years). In Churg’s study, patients with a fibrotic NSIP or UIP pattern had a poor prognosis (median survival of 2.1 and 2.8 years respectively). In comparison, the prognosis of patients with a pattern of only peribronchiolar fibrosis was much better (median survival of 11.3 years).

**Differential Diagnosis:**

The pathologic differential diagnosis includes sarcoidosis, organizing pneumonia pattern, fibrosing nonspecific interstitial pneumonia pattern, usual interstitial pneumonia (UIP) pattern, granulomatous infections, lymphoid interstitial pneumonia (LIP), and drug reactions (tables 3a and 3b). In contrast to hypersensitivity pneumonitis, the granulomas of sarcoidosis are large, well defined and have a lymphatic, rather than strictly a peribronchial distribution. There is also usually no or little interstitial infiltrate in sarcoidosis. Genuine cases of hypersensitivity pneumonitis may show a predominantly organizing pneumonia pattern, fibrotic NSIP pattern and UIP. However, most of these cases will show foci of poorly formed granulomas, giant cells or Schaumann bodies. Nonetheless, these features will be absent in some cases and in the appropriate clinical setting, the possibility of hypersensitivity pneumonitis should nonetheless be raised.

The infiltrate in LIP diffusely involves the lung and is denser than in hypersensitivity pneumonitis. While multinucleated giant cells may be present, they are often inconspicuous and overshadowed by the interstitial infiltrate. Drugs may occasionally cause a granulomatous interstitial pneumonitis. The best known example is methotrexate, but other drugs such as nitrofurantoin may also cause this reaction pattern. Clinical correlation is thus mandatory in most cases to exclude a drug reaction.

**Pathogenesis:**

HP represents a combination of immune complex-mediated (type III) and T-cell-mediated, delayed (type IV) hypersensitivity reactions which involves the production of multiple cytokines. Recent studies have postulated that individuals with a relatively stronger $T_H1$ (as opposed to $T_H2$) lymphocytic response to antigen stimulation are more at risk for developing hypersensitivity pneumonitis presumably reflecting different profiles of cytokine expression. Jinta, et al showed an increased number apoptosis of epithelial cells in patients with chronic hypersensitivity pneumonitis having a UIP
pattern compared to patients with a NSIP pattern. Based on these observations, they suggested that augmented epithelial apoptosis may contribute to the development of UIP like patterns of fibrosis in chronic hypersensitivity pneumonitis.31

**Prognosis / Treatment:**

If recognized, the prognosis of acute or subacute cases of hypersensitivity pneumonitis is generally good. Optimal treatment consists of the identification and avoidance of the agent eliciting the disease. If this is not possible, or the inciting agent cannot be identified, then treatment with steroids is often beneficial. In as many as two thirds of cases with the classic histologic features of hypersensitivity pneumonitis (bronchiolocentric chronic interstitial pneumonia, small loosely formed granulomas, foci of OP) the inciting antigen cannot be identified. Interestingly, however, even in these cases the prognosis is generally good.17 Unfortunately, for unknown reasons, a few patients will go on to develop progressive interstitial fibrosis even with avoidance of the antigen.13 Patients who present with more chronic disease and have a fibrotic NSIP or UIP pattern typically have a worse prognosis.23,25
## Table 1.

**Agents of hypersensitivity pneumonitis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Occupation</th>
<th>Antigen</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer's Lung</td>
<td>Dairy farmers</td>
<td><em>Micropolyspora faeni</em></td>
<td>Moldy hay</td>
</tr>
<tr>
<td>Grain handler's lung</td>
<td>Grain handlers</td>
<td><em>Thermoactinomyces faeni</em></td>
<td>Moldy grain</td>
</tr>
<tr>
<td>Bagassosis</td>
<td>Sugar cane workers</td>
<td><em>Thermoactinomyces sacchari</em></td>
<td>Sugar cane</td>
</tr>
<tr>
<td>Humidifier lung</td>
<td>May cause sick building or home syndrome</td>
<td>various ameba, fungi, and bacteria</td>
<td>Water reservoirs</td>
</tr>
<tr>
<td>Detergent worker's lung</td>
<td>Detergent workers</td>
<td><em>Bacillus subtilis</em></td>
<td>Enzymes in detergent</td>
</tr>
<tr>
<td>Suberosis</td>
<td>Cork workers</td>
<td><em>Penicillium frequentans</em></td>
<td>Moldy cork dust</td>
</tr>
<tr>
<td>Cheese worker's lung</td>
<td>Cheese workers</td>
<td><em>Penicillium casei</em></td>
<td>Cheese mold</td>
</tr>
<tr>
<td>Malt worker's lung</td>
<td>Barley workers</td>
<td><em>Aspergillus clavatus</em></td>
<td>Moldy grains</td>
</tr>
<tr>
<td>Bird fancier's lung</td>
<td>Poultry and bird handlers</td>
<td>Bird proteins</td>
<td>Bird serum, feathers, and excreta</td>
</tr>
<tr>
<td>Condition</td>
<td>Occupation</td>
<td>Cause</td>
<td>Source</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Rodent handler's lung</td>
<td>Laboratory animal handlers</td>
<td>Rat proteins</td>
<td>Rat urine and serum</td>
</tr>
<tr>
<td>Maple bark stripper's lung</td>
<td>Woodworkers</td>
<td>Cryptostroma corticale</td>
<td>Moldy bark</td>
</tr>
<tr>
<td>Mushroom worker's lung</td>
<td>Mushroom workers</td>
<td>Thermophilic bacteria</td>
<td>Compost</td>
</tr>
<tr>
<td>Machine operator's lung</td>
<td>Metalworkers</td>
<td>Various bacteria and fungi</td>
<td>Aerosolized metal working fluid</td>
</tr>
<tr>
<td>Soybean worker's lung</td>
<td>Soybean workers</td>
<td>Soybean</td>
<td>Soybean hulls</td>
</tr>
<tr>
<td>Sequiosiosis</td>
<td>Redwood workers</td>
<td>Aureobasidium, Graphium</td>
<td>Redwood sawdust</td>
</tr>
<tr>
<td>Tobacco worker's lung</td>
<td>Tobacco workers</td>
<td>Aspergillus species</td>
<td>Mold on tobacco</td>
</tr>
<tr>
<td>Wine grower's lung</td>
<td>Wine growers</td>
<td>Botrythis cinerea</td>
<td>Mold on grapes</td>
</tr>
<tr>
<td>Summer-type HP</td>
<td>Not applicable</td>
<td>Trichosporon cutaneum</td>
<td>Yeast in homes</td>
</tr>
<tr>
<td>Chemical worker’s lung</td>
<td>Plastic workers</td>
<td>Trimellitic amhydride Tolune-diisocyanate Diphenyl-methane diisocyanate</td>
<td>Plastic, paint, polyurethane</td>
</tr>
</tbody>
</table>
Table 2a: Histologic Features – Subacute phase of Hypersensitivity Pneumonitis

Major:
- Chronic interstitial pneumonia with peribronchiolar accentuation (may be predominant feature = cellular NSIP)
- Small non-necrotizing granulomas (may be absent in 30 to 80% of cases)
- Foci of organizing pneumonia (may be predominant feature)

Minor:
- Foamy macrophages within alveolar air spaces
- Giant cells may contain cholesterol clefts, asteroid bodies, calcium oxalate crystals, or Schaumann bodies.
- Foci of neutrophils (rarely)

Table 2b: Histologic Features – Chronic phase of Hypersensitivity Pneumonitis

- Fibrotic NSIP pattern
- UIP pattern
- Peribronchiolar fibrosis
- Poorly formed granulomas (may be absent)
- Multinucleated giant cells (may be absent)
- Schaumann bodies
Table 3a: Hypersensitivity Pneumonitis – Subacute Phase: Differential Diagnosis

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Hypersensitivity Pneumonitis</th>
<th>Sarcoidosis</th>
<th>Lymphocytic Interstitial Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>2/3 of open biopsies</td>
<td>100% of cases</td>
<td>5-10% of cases</td>
</tr>
<tr>
<td>Morphology</td>
<td>Poorly-formed</td>
<td>Well-formed</td>
<td>Well-formed or poorly-formed</td>
</tr>
<tr>
<td>Distribution</td>
<td>Mostly random, some peribronchiolar</td>
<td>Lymphangitic, peribronchiolar, perivascula</td>
<td>Random</td>
</tr>
<tr>
<td>Intraluminal fibrosis</td>
<td>2/3 of open biopsies</td>
<td>Very rare</td>
<td>Unusual</td>
</tr>
<tr>
<td>Lymphocyte infiltrates</td>
<td>Mild-moderate, peribronchiolar</td>
<td>Absent or minimal</td>
<td>Extensive, diffuse</td>
</tr>
<tr>
<td>Dense fibrosis</td>
<td>In advanced cases</td>
<td>In advanced cases</td>
<td>Unusual</td>
</tr>
<tr>
<td>BAL Lymphocytosis</td>
<td>CD8&gt;CD4</td>
<td>CD4&gt;CD8</td>
<td>Usually B-cells</td>
</tr>
<tr>
<td>Histologic Feature</td>
<td>Hypersensitivity Pneumonitis</td>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>Fibrotic NSIP</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Granulomas, giant cells, Schaumann bodies</strong></td>
<td>80 -90% of open biopsies</td>
<td>Usually none</td>
<td>Usually none</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Rare, poorly formed, or single giant cells or Schaumann bodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Mostly random, some peribronchiolar</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Areas of subacute hypersensitivity pneumonitis</strong></td>
<td>Present in half of biopsies</td>
<td>Absent</td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>Peribronchiolar fibrosis</strong></td>
<td>Often present</td>
<td>Often absent or inconspicuous</td>
<td>Often absent or inconspicuous</td>
</tr>
</tbody>
</table>
References: