Pulmonary Alveolar Proteinosis

Σπύρος Α Παπίρης
PAP

- Rosen SH, Castleman B and Liebow AA.

**PAP**
* N Engl J Med 1958

- Rare disorder in which lipoproteinaceous material accumulates within alveoli
- Variable clinical course from respiratory insufficiency to spontaneous resolution
- Susceptibility to pulmonary infections
PAP

History

• Dr. Benjamin Castleman of the Massachusetts General Hospital recognized the first case of this series in July 1953

• Linell and associates from Sweden described the case of a 57-year-old man who had been symptomatic since 1946 and died of disseminated cryptococcosis in June 1951


• 1957 description of a woman with marked thrombocytosis caused by an underlying myeloproliferative disorder, where acellular eosinophilic “intra-alveolar coagulum”, first described case of PAP occurring as a “secondary” phenomenon to an underlying hematologic malignancy

PAP
(prevalence 0.37 per 100,000)

• CONGENITAL
(mutations in the genes encoding surfactan protein B or C or the βc chain rGM-CSF)

• SECONDARY
[conditions involving functional impairment or reduced numbers of AMs (hematologic cancers, pharmacologic immunosuppression, inhalation of inorganic dust or toxic fumes, infections)]

• ACQUIRED (90%)
(autoimmune disorder, Abs against GM-CSF)
State of the Art

Pulmonary Alveolar Proteinosis
Progress in the First 44 Years

John F. Seymour and Jeffrey J. Presnell

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 410)</th>
<th>Male (n = 292)</th>
<th>Female (n = 110)</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (I.Q. range)*</td>
<td>n</td>
<td>Median (I.Q. range)*</td>
</tr>
<tr>
<td>Age, years</td>
<td>408</td>
<td>39 (30–46)</td>
<td>292</td>
<td>39 (32–47)</td>
</tr>
<tr>
<td>Duration of symptoms/CXR changes, mo</td>
<td>288</td>
<td>7 (3–19)</td>
<td>216</td>
<td>7 (3–23)</td>
</tr>
<tr>
<td>African American race‡</td>
<td>144</td>
<td>17</td>
<td>111</td>
<td>15</td>
</tr>
<tr>
<td>Nonsmoker§</td>
<td>168</td>
<td>28</td>
<td>114</td>
<td>15</td>
</tr>
<tr>
<td>Mode of diagnosis†</td>
<td>360</td>
<td>266</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Autopsy</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Open biopsy</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Transbronchial biopsy</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>BAL</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Elevated hemoglobin§</td>
<td>97</td>
<td>21</td>
<td>78</td>
<td>19</td>
</tr>
<tr>
<td>Elevated LDH**</td>
<td>77</td>
<td>82</td>
<td>53</td>
<td>81</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>159</td>
<td>60 (46–70)</td>
<td>116</td>
<td>60 (48–69)</td>
</tr>
<tr>
<td>[A–a]DO₂, mm Hg†</td>
<td>131</td>
<td>48 (34–60)</td>
<td>96</td>
<td>49 (33–60)</td>
</tr>
<tr>
<td>Therapeutic lavage,‡</td>
<td>312</td>
<td>54</td>
<td>214</td>
<td>52</td>
</tr>
</tbody>
</table>
DYSPNOEA is the most common presenting symptom. It usually occurs on moderate exertion but in a few patients occurs at rest. COUGH is the other common symptom. These symptoms are often trivial and some patients do not present until they develop a supervening infection. This may explain the acute onset of symptoms and fever observed in some patients. A LOW GRADE FEVER may also occur as a consequence of pulmonary alveolar proteinosis in the absence of secondary infection.
“Crazy-Paving” Pattern at Thin-Section CT of the Lungs: Radiologic-Pathologic Overview

Santiago E. Rossi, MD • Jeremy J. Erasmus, MD • Mariano Volpacchio, MD • Tomas Franquet, MD • Teresa Castighioni, MD • H. Page McAdams, MD
CAUSES

INFECTION
- Pneumocystis carinii pneumonia (PCP)

NEOPLASM
- Mucinous Bronchioloalveolar Carcinoma (BAC)
- Pulmonary Alveolar Proteinosis (PAP)
- Sarcoidosis
- Nonspecific Interstitial Pneumonia (NSIP)
- Organizing Pneumonia (OP)

IDIOPATHIC
- Lipoid Pneumonia

INHALATION

SANGUINEOUS
- Adult respiratory distress syndrome (ARDS)
- Pulmonary Hemorrhage Syndromes
open-lung biopsy the “gold standard”
PAP BAL
PAP
Natural History

• Stable but with symptoms
• Progressive deterioration
  • Spontaneous improvement?? (8%)

• Deaths (75% respiratory failure, 20% infections)
PAP complications

- The major complication of pulmonary alveolar proteinosis is infection with unusual organisms such as *Aspergillus* species, *Nocardia* species, *Mycobacterium* species, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis carinii*, and viruses.
### Opportunistic Pathogen

*Mycobacterium tuberculosis*

MAIC

*Streptomyces spp.*

*Cryptococcus spp.*

*Nocardia spp.*

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*Mucorales*

*Histoplasma spp.*

*Coccidioides immitis*

*Aspergillus spp.*

*Blastomyces dermatitidis*

*Acinetobacter spp.*
The first advance in the treatment of PAP came in November 1960, when Dr. José Ramirez-Rivera at the Veterans’ Administration Hospital in Baltimore applied repeated “segmental flooding” as a means of physically removing the accumulated alveolar material. Following 30 mg of oral codeine, and without other sedation or anesthesia, a percutaneous transtracheal endobronchial catheter of 1.17-mm external diameter was positioned “blindly.” Through this catheter, aliquots of 100 ml of warmed saline were instilled at a rate of 50–60 drops per minute. This usually initiated a bout of “45 to 70 minutes of violent coughing,” which typically produced “30–40 ml of white viscid material,” and was repeated four times a day for 2–3 weeks using physical positioning to direct the saline sequentially into different lung segments.
The overall prognosis for alveolar proteinosis treated by whole lung lavage is excellent. There are also several reports of spontaneous resolution, and series prior to the introduction of whole lung lavage quote spontaneous improvement in up to 25% of patients.
Figure 8. Overall survival from the time of diagnosis of acquired PAP was significantly improved if patients had received therapeutic lavage at any time during their disease course (lavage, n = 146; no lavage, n = 85, p = 0.044).
A few patients require more than six cycles of lung lavage. A small proportion (<15%) require lavage every six months to maintain their functional status and fewer than 10% are non-responders.

Figure 10. Duration of response to therapeutic lavage for patients with acquired PAP (median = 15 months; n = 55).
Pulmonary Alveolar Proteinosis*

Treatment by Bronchofiberscopic Lobar Lavage

Shih-Lung Cheng, MD; Hou-Tai Chang, MD; Hon-Ping Lau, MD; Li-Na Lee, MD, PhD; and Pan-Chyr Yang, MD, PhD, FCCP

*(CHEST 2002; 122:1480–1485)*
5–9 μg/kg/day

GM-CSF THERAPY IN ACQUIRED PAP

(A) Case 1 pre  Case 1 post

(B) Case 2 pre  Case 2 post

(C) Case 3 pre  Case 3 post

(D) Before treatment  After treatment
PAP

A true pathophysiologic “cure” or the persistence of subclinical disease???

Although it is clear that the disease process of PAP eventually enters a quiescent state in most surviving patients, either without therapeutic intervention, or following a period of variable duration where therapeutic lavage is required, it is unclear whether the underlying pathophysiologic process is reversed, or simply reduced in severity to such a degree that clinical, radiographic, and functional consequences are minimized.