Pulmonary alveolar proteinosis and pulmonary cryptococcosis in an adolescent boy

A 14-year-old boy received massive lung lavage for pulmonary alveolar proteinosis after transtracheal catheter lavage was ineffective in alleviating progressive respiratory failure. He then developed widespread pulmonary cryptococcosis which was apparently eradicated by the administration of amphotericin B. Two years later, both lungs were again washed because of rapidly decreasing vital capacity. Presently, at age 17 years, he appears healthy although pulmonary function is less than normal.


Pulmonary alveolar proteinosis (PAP) rarely occurs in children. We are aware of 34 pediatric case reports (15 years of age or less) in the world literature. Of 190 adult patients with PAP, two cases with associated cryptococcosis have been reported, both of whom died. We wish to report the case of a boy with PAP complicated by cryptococcosis, who has apparently recovered after treatment with lung lavage and amphotericin B.

CASE REPORT

Patient N. W. (14 years of age) developed a nonproductive cough and increasing dyspnea on exertion in late 1967. By April, 1968, he had lost 20 pounds. Chest radiographs revealed an extensive patchy infiltrate that radiated from both hila with sparing of the apices, with air bronchograms, and normal cardiac silhouette (Fig. 1A). Sputum cultures yielded no significant organisms. Intradermal skin tests for tuberculosis and fungi were negative. He did not improve following treatment with expectorant, antibiotic, or bronchodilating agents or physiotherapy.

Thoracotomy was then performed which revealed a consolidated lung with yellowish mottling. Following biopsy from the right lower lobe, yellow material exuded from needle holes during suturing. On histologic examination (Fig. 2) the appearance was consistent with PAP as originally described by Rosen and associates. No pathologic organisms were found in the tissues.

On May 14, 1968, the patient was transferred to Doernbecher Memorial Hospital for children. He had facial plethora and nailbed cyanosis but no digital clubbing. The respiratory rate at rest was 30 per minute. Walking on the level caused dyspnea, although the chest was free of rales.

Laboratory studies. Hematocrit was 59 per cent, hemoglobin 18 Gm. per 100 ml., and white blood count and differential were normal. Erythrocyte sedimentation rate, renal, liver, thyroid, and adrenal function tests were normal. Pulmonary function studies demonstrated restrictive impairment (Table I). Blood gas determinations showed arterial hypoxemia, hypocapnia, and normal pH. Serum lactic dehydrogenase was 218 units (normal = 100 to 120).
Serum electrolytes, fasting blood glucose, calcium, phosphorus, cholesterol, total lipids, alpha-1 antitrypsin values, and coagulation studies were normal. Cryoglobulin was not found. Protein electrophoresis demonstrated a slight elevation of alpha-1 and 2 and gamma globulins. Immunoelectrophoresis and the beta-1C component of complement were normal. Lupus erythematosus preparations, heterophil antibody, cold agglutinins, and Venereal Disease Research Laboratory serologies were negative. Blood urea nitrogen and routine urinalysis were not remarkable. Mumps antigen skin test was positive.

**Therapy.** On May 25, 1968, a plastic catheter was inserted through the cricothyroid membrane to a bronchus. Fifty milliliters of sterile 0.9 per cent NaCl (N/S) was instilled through the catheter four times daily, causing hyperpnea and coughing. Small quantities of sputum were coughed up from which flocculant white material precipitated which contained lactic dehydrogenase isozymes, 2, 3, and 4, identified by starch gel electrophoresis. The addition of 250 units of heparin to N/S on alternate days retarded precipitation of the sediment but did not increase sputum production. His condition continued to deteriorate and after five weeks the catheter was removed.

Massive pulmonary lavage was then performed under general anesthesia as described by Ramirez-R." During the initial lavage of the left lung, he had a period of severe respiratory acidosis.

The procedure was stopped and the arterial blood gas values returned to normal. The lavage effluent was creamy white and a thick sediment was easily separated. A heavy growth of Serratia species was identified on culture; polymyxin B was therefore given parenterally until subsequent cultures were negative for Serratia.

Six days later, the right lung was lavaged without complications, using a total of 5,500 c.c.
Table I. Vital capacity and blood gas studies in relation to therapy

<table>
<thead>
<tr>
<th>Date</th>
<th>Vital capacity (ml.)</th>
<th>Hematocrit (%)</th>
<th>Arterial</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11-68</td>
<td>1,725</td>
<td>59</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>6-26-68</td>
<td>1,440</td>
<td>57</td>
<td>35.8</td>
<td>35.5</td>
</tr>
<tr>
<td>7-12-68</td>
<td>2,220</td>
<td>47</td>
<td>75</td>
<td>33.5</td>
</tr>
<tr>
<td>11-11-69</td>
<td>3,200</td>
<td>47</td>
<td>75</td>
<td>33.5</td>
</tr>
<tr>
<td>9-23-70</td>
<td>2,250</td>
<td>57</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>11-25-70</td>
<td>2,540</td>
<td>54</td>
<td>63</td>
<td>30</td>
</tr>
</tbody>
</table>

*Total lung capacity increased by 800 ml. Predicted vital capacity = 4,800 ml. at 17 years.*

...
after 14 months; however, antibody against Cryptococcus was rarely detected.

After completion of treatment, vital capacity and arterial blood gases slowly improved (Table 1). During the next 18 months, the patient continued to have dyspnea with heavy exercise but was otherwise asymptomatic. On radiographs the nodular mottling of the lungs gradually changed to the homogeneous fluffy appearance consistent with PAP.

In the summer of 1970, the symptoms of respiratory insufficiency became progressively more troublesome. Massive lavages with N/S were performed in October, 1970, using 8½ liters in the left lung and 14 liters in the right lung 3 weeks later. After the first lavage, he developed a bronchopneumonia due to a Hemophilus species for which he was treated with ampicillin. He had no problems after the right (second) washing.

As of January, 1971 (about 40 months after onset of his illness), arterial gas values, lung function measurements, and chest radiographs showed improvement, but not as dramatic as that which followed the lavages of 1968. He was 17 years of age and had re-entered high school.

**DISCUSSION**

Predominantly a disease of males, PAP has been reported in patients from one month to 79 years of age with peak incidence between 30 and 50 years. There is no correlation of PAP with occupation, smoking, or other inhalants, race, nationality, or geographic location. Many asymptomatic adults have been diagnosed after a pulmonary infiltrate was noted on a routine chest radiograph. PAP may be associated with hematologic disorders, immune deficiency states, and tuberculosis, but occurs rarely with silicosis. It has never been reported with sarcoidosis.

Prior to the use of lavage therapy, about 40 per cent of the adult patients recovered or remained asymptomatic, 22 per cent remained symptomatic but nonprogressive, and the remainder progressed to death from either cardiopulmonary failure or complications. The mortality rate among children has been over 75 per cent (of 34 patients, 26 died).

During the five years immediately following delineation of PAP, 18 cases with associated mycotic infection were reported, including aspergillus, mucormycosis, and nocardia. Cryptococcus has been commonly identified in sputum samples but appeared to be a pathogen in only three instances. In several patients, fungi could not be identified until just prior to death or at autopsy. Two patients had nocardiosis of the central nervous system without concurrent involvement of the lungs.

Of the 27 patients (including our patient) with PAP and mycosis, 16 did not receive adrenal corticosteroids. Of the 11 who were treated with steroids, a few received them only just prior to death. There were also 38 patients treated with adrenal steroids who did not develop mycosis. It therefore seems unlikely that the course of the mycosis was significantly affected by adrenal corticosteroids. Although these drugs are rarely beneficial in treatment of PAP, they probably should not be withheld when they might otherwise be utilized, as in certain patients with associated leukemia.

Patients with PAP have been treated with a variety of mycolytic, proteolytic, and expectorant drugs, antibiotics, and diuretics, but these have been of uncertain value. In 1963, Ramirez-R and associates reported some improvement over several months when a technique of transtracheal catheter lavage was used, although several of his more incapacitated patients had difficulty. This is essentially the same procedure that we used for five weeks in our patient.

In 1966, Ramirez-R reported benefits from massive lavage using the Carlens double lumen catheter. Since then, several other
authors have reported similar success with this technique.\textsuperscript{37, 39, 40} It is clear that massive lung lavage is not a benign procedure. Fluid spillover into the oxygenated lung may occur, leading to an acute respiratory acidosis, as we think occurred with the first washing in our patient. A severely compromised patient may not tolerate even the temporary deprivation of the use of the lung being treated. Sepsis may result from the bacteremia that occurs during lavage or a localized infection may be spread throughout the lungs.\textsuperscript{32–34} Fluid and electrolyte imbalances are also theoretical hazards. Pulmonary arteriovenous shunting may cause severe arterial hypoxemia during the emptying phase of each washing cycle.\textsuperscript{3} Cardiac dysrhythmias, atelectasis, hypotension, or pulmonary bleeding may occur.

Despite the hazards, most patients with PAP who are treated by lung lavage are greatly improved. A patient may spontaneously recover from severe symptoms without definitive therapy, but prolonged incapacitation seems undesirable. Massive lavage probably should be used in patients with PAP who have progressive or stable, but incapacitating, cardiorespiratory dysfunction.

There is no firm evidence that either heparin or N-acetyl-cysteine are helpful in the concentrations which have been used. The effectiveness of lavage is probably the result of mechanical suspension of the sediment in the saline rather than chemical dissolution of the material.

**Sediment analysis.** Rosen and associates\textsuperscript{1} first found that the concentration of lipid in PAP lung tissue was five to seven times that in control lung tissue. Later reports confirmed this and indicated that phospholipids in particular are elevated in the alveolar material.

Stansifer and Bourgeois\textsuperscript{46} identified several lipids and proteins in alveolar material from the lung of an infant with PAP, which they suggested was a serum transudate. Larson and Gordinier\textsuperscript{47} suggested that PAP phospholipid is pulmonary surfactant, and that this syndrome results from either overproduction or impaired clearance of surfactant from the alveoli. However, subsequent studies on PAP material have shown variable surface tension activity.\textsuperscript{38, 39}

Hawkins and associates\textsuperscript{38} demonstrated that the immunoproteins recovered from washings are from the serum. Ramirez-R and Harlan\textsuperscript{39} found the major lipid component of PAP effluent to be palmitoyl lecithin, which they considered to be surfactant. Using C-14 and H-3 radiolabeled fatty acids, they were unable to find significant alterations in the metabolic pathways of phospholipid synthesis and concluded that PAP results from prolonged alveolar retention of metabolites produced by the lining cells. This concurred with an earlier observation that intravenously administered dye became bound to the PAP material and was recoverable months later.\textsuperscript{40}

Analysis of combined lavage effluents (first series) from our patient is depicted (Table II and Fig. 3). On the basis of these findings and the results of other investigators, we concluded that some of the PAP material is produced by the lung parenchyma and some is a transudate from the capillaries, with delayed or blocked clearance of all of its identified components.

There may be subtle membrane damage in the walls of the affected alveoli. Altered alveolar-capillary membrane permeability may result from a variety of causes, including changes in intrathoracic pressure. An acquired enzyme defect which might explain impaired alveolar clearing remains to be
Table II. Analysis of lavage effluent

<table>
<thead>
<tr>
<th>Protein concentrations</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>3.7 mg./ml.</td>
</tr>
<tr>
<td>α-1 antitrypsin</td>
<td>0.38</td>
</tr>
<tr>
<td>IgG</td>
<td>1.9</td>
</tr>
<tr>
<td>IgA</td>
<td>0.3</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Detectable</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>Detectable</td>
</tr>
</tbody>
</table>

| Lipid percentages      |            |
| Phospholipids          | 72.5%      |
| Neutral lipids         | 27.5%      |

Analysis by Drs. J. Clements and F. Kueppers.

identified. Elevated serum lactic dehydrogenase enzyme activity has been reported frequently but is not unique to PAP. Kuhn and associates found a generalized increase in activity of eight alveolar wall enzymes studied histochemically.

One of the most striking features of PAP is the lack of cellular response by the host to the material occupying the alveolar spaces. Luminal cellular exudates are unusual and alveolar macrophage activity is not particularly increased. Spitler and colleagues found no impairment of in vitro macrophage migration on exposure to the lavage sediment from our patient.

Pulmonary alveolar proteinosis may be one pathologic expression common to a variety of underlying pulmonary diseases, and there may be limited involvement of the lungs without symptomatology. The process is limited to the alveoli with minimal modification of the parenchymal architecture. When spontaneous remission occurs, there may be no residual lung damage, so that the condition is amenable to massive lung lavage. Intercurrent mycotic infection is a distinctive feature and an ongoing hazard. The events initiating and perpetuating PAP remain obscure.

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