the age of 52 years, was experiencing relatively excellent health. One of their conclusions merits repetition: “In the case of the latter (the individual subject), it is shown that the reparative processes of human protoplasm, even when not subjected to medical or surgical interference, may be striking.” Amen. The patient reported here was enjoying good health at the age of 86 years, being untroubled by his dynamically mild mitral valve disease. In this he was by no means unique; but it is an observation that merits re-emphasis from time to time.

ACKNOWLEDGMENT: I am indebted to Dr. Samuel P. Asper, Vice President for Medical Affairs, The Johns Hopkins Hospital, for his help in identifying the initials and handwriting of Dr. William S Thayer. Dr. Thayer was Chief Resident Physician at Johns Hopkins from 1891 to 1898, a position reserved for men of exceptional ability and favorable promise. He subsequently wrote an article about Osler.2

REFERENCES

Pulmonary Interstitial Fibrosis Following Alveolar Proteinosis*

Arnold R. Hudson, M.D.;** Gerald M. Halprin, M.D.;† James A. Miller, M.D.;‡ Kaye H. Kilburn, M.D.||

Whether permanent structural lung changes follow pulmonary alveolar proteinosis (PAP) is not known. A patient with PAP, but with no evidence of lung fibrosis, became asymptomatic spontaneously. However, 13 years after the onset of his illness he died from pulmonary insufficiency due to lung fibrosis. This suggests that the typical histologic picture of PAP is only a stage of a disease in which the end stage is fibrosis.

There are several reports of pulmonary interstitial fibrosis or alveolar septal cellular infiltrate associated with pulmonary alveolar proteinosis (PAP).1-10 Some authors2-4 suggest that PAP may precede fibrosis. However, there is only one case report of serial lung biopsies in a patient clearly establishing the onset of PAP prior to the onset of fibrosis.2 Other reports of fibrosis associated with PAP have been obscured by lung infections or other factors that could cause fibrosis.3-7,10 The impression that fibrosis and PAP are only coincidental is supported by observations that the lipoproteinaceous material may remain in alveoli for years without eliciting a cellular reaction.11

This report concerns a patient whose lung biopsy showed typical PAP without thickening or inflammatory cellular infiltrate of alveolar septa. Twelve years subsequent to this biopsy he died of pulmonary insufficiency secondary to lung fibrosis. There was no occupational exposure to account for the fibrosis.

CASE REPORT

A black construction worker was well until 1959, when at 45 years of age he experienced an acute illness characterized by cough, shortness of breath, fever and generalized arthralgias. He was hospitalized and treated for “pneumonia.” On a subsequent admission in 1960 an open biopsy of the right lung was interpreted as alveolar proteinosis. From 1961 to 1967 the patient resided in Southern California and was asymptomatic without therapy. During the interval he did not visit a doctor, consequently no chest x-ray film was obtained. In 1968 he noted mild dyspnea when walking up hills. Subsequently dyspnea worsened and he discontinued work in May, 1971. On first admission to the Durham Veterans Administration Hospital in October, 1971 he described three-pillow orthopnea, persistent nonproductive cough, shortness of breath at rest, nightly paroxysmal nocturnal dyspnea and a 11.3 kg weight loss. He had smoked one package of cigarettes per day for 30 years. A lifetime occupational inventory included employment as a cook and a construction laborer. He never worked in a factory or a mine and was unaware of any exposure to silica or asbestos. Physical examination on admission revealed a well-developed, well-nourished black man in no acute distress. He had a nonproductive cough. His temperature was 36.6°C, pulse rate 84/min, respiration rate 32/min, and blood pressure was 100/80 mm Hg. Chest expansion and diaphragm excursions were reduced. There was mild clubbing of the nail beds. The remainder of the physical examination showed no abnormalities.

Figure 1. Posteroanterior chest roentgenogram in November, 1971, showing reduced lung volumes and diffuse interstitial infiltrates.

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700 Hudson ET AL

CHEST, 65: 6, JUNE, 1974

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Table 1—Pulmonary Function Studies

<table>
<thead>
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<th></th>
<th>Predicted, 10/27/71</th>
<th>Measured, 3/1/72</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>4.15</td>
<td>1.73 liters</td>
</tr>
<tr>
<td>RV</td>
<td>0.93</td>
<td>0.93 liters</td>
</tr>
<tr>
<td>TLC</td>
<td>5.91</td>
<td>2.66 liters</td>
</tr>
<tr>
<td>FEV1.0</td>
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<td>1.34 liters</td>
</tr>
<tr>
<td>MMF</td>
<td>3.0</td>
<td>1.23 liters/sec</td>
</tr>
<tr>
<td>PaO2 mm Hg</td>
<td>69</td>
<td>39</td>
</tr>
<tr>
<td>D(A-a)O2 mm Hg</td>
<td>50</td>
<td>64</td>
</tr>
<tr>
<td>D12CO (ml/min/mm Hg)</td>
<td>16.5</td>
<td>9.8</td>
</tr>
<tr>
<td>steady state (resting)</td>
<td></td>
<td>5.4</td>
</tr>
</tbody>
</table>

A chest x-ray film demonstrated a diffuse interstitial infiltrate (Fig 1). The hemoglobin, hematocrit and white blood cell count, urinalysis and electrocardiogram were normal. The lactic acid dehydrogenase values ranged from 218 to 360 (normal values 90-184). A histoplasmin skin test produced 11 mm of induration at 48 hours and the intermediate tuberculin test was negative at 48 hours. Serum complement fixation tests for blastomycosis, coccidioidomycosis, histoplasmosis and aspergillosis were negative. Sputum cultures for bacteria, fungi and tuberculosis were negative. Serum protein electrophoresis revealed a heterogenous increase in the gamma globulins. Needle biopsy of the liver yielded normal findings. Pulmonary function studies showed a greatly reduced total lung capacity, moderately reduced expiratory flow (MMF), moderate hypoxemia (PaO2 69 mm Hg), wide alveolar arterial oxygen difference, and low diffusing capacity for carbon monoxide (Table 1).

The lung biopsy specimen taken in 1960 was obtained, and new sections were studied (Fig 2). (Chest films were not available.) The diagnosis of alveolar proteinosis was verified. Bronchopulmonary lavage of the left lung was performed Nov 11, 1971. Lavage fluid sediment revealed polymorphonuclear leukocytes, macrophages, mucous threads and eosinophilic material. On November 19, an open biopsy of the right lung was interpreted as mild interstitial fibrosis, and no PAS-positive material was present within the alveoli.

On Feb 8, 1972, he was hospitalized at another hospital for continuous abdominal pains and edema of the lower extremities. Edema was reduced by treatment with digitalis, diuretics and intermittent positive pressure breathing with saline solution, and the gastrointestinal symptoms improved. He was transferred to the Durham VA Hospital Feb 17, 1972, for further management. On admission he was afebrile, pulse was 80/min, with a bigeminal rhythm, and his blood pressure was 120/80 mm Hg. There was central cyanosis. Neck veins were distented to 4 cm above the clavicle at 45°. Inspiratory coarse rales were heard over the entire chest. There was a loud third sound at the left sternal border and apex but no murmurs or rubs. Liver size by percussion was 14 cm in the midclavicular line. There was 1+ pretibial pitting edema and mild clubbing of the nail beds. The remainder of the physical examination was normal.

The blood cell count and urinalysis were normal. Chest x-ray films showed cardiomegaly but no change in the pulmonary infiltrates. Analysis of arterial blood gases on admission
revealed severe hypoxemia, a normal arterial carbon dioxide tension (PaCO₂), and a normal pH (Table 1). Sputum cultures for bacteria, fungi and tuberculosi were negative. An electrocardiogram showed right atrial enlargement, right axis deviation, decreased voltage in the limb leads and left ventricular ischemia. He was treated with a seven-day course of tetracycline followed by five days of cephalothin sodium (Keflin) 8 gm/day intravenously and kanamycin sulfate 1 gm/day intramuscularly empirically without benefit. Despite a 4.52 kg weight loss by diuresis and a trial of 60 mg/day of prednisone therapy for one week, no improvement was observed in symptoms or arterial blood gas levels. On May 26, he became hypotensive and died.

At necropsy the lungs were densely fibrotic with paracartial emphysema and traction bronchiectasis resulting in a honeycombed appearance. Microscopic examination revealed severe interstitial fibrosis (Fig 3), chronic bronchitis and focal entrapment of abundant mucoid bronchiolar fluid with a scanty amount of similar alveolar fluid, which stained positive both with PAS and alcan blue. Despite a careful search, PAP was not found. Other findings included: right ventricular hypertrophy and biventricular dilation of the heart and chronic passive congestion of the liver.

**DISCUSSION**

In the original description of PAP by Rosen et al., an increase in the number of alveolar septal inflammatory cells was noted in cases 11 and 18. Case 2 from that series, reported in more detail elsewhere, demonstrated mild fibrosis on initial lung biopsy followed by more extensive fibrosis 9 months later at postmortem. The initial lung biopsy from case 7 showed typical PAP and was free from inflammatory reaction or fibrosis. Two and one-half years later when the patient was asymptomatic a third lung biopsy demonstrated mild fibrosis and nearly complete clearing of the alveolar material. Such a sequence of histologic changes could be due to exposure to an agent such as silica dust. Rodents exposed to silica dust for several weeks and human beings employed as sandblasters for a few years have developed pathologic lung changes very similar to PAP with slight fibrosis. Whether the PAP stimulates interstitial fibrosis characteristic of chronic lung reaction to silica dust is unknown. The biopsy area in the present case showed no inflammatory reaction or fibrosis initially but 12 years later the patient died of severe interstitial fibrosis. No evidence of an infectious process was present, and no significant exposure to silica could be established.

The natural history of alveolar proteinosis may follow several pathways. Death may result directly from respiratory failure as early as two months from onset. The process may completely resolve without therapy or remain unchanged for as long as 20 years. Serious complicating infections such as Aspergillus, Nocardia, Cryptococcus or Mucormycosis may result in a fulminating course. Observing the natural history of PAP may now be more difficult because of intervention with bronchopulmonary lavage. It is not clear whether all patients with PAP should undergo lavage. However, bronchopulmonary lavage may prove beneficial not only by relieving the respiratory distress due to alveolar filling, but also by improving the lungs' defense mechanisms against infection and fibrosis by removing bronchiolar plugs, thus improving alveolar clearance. Long-term observation of patients, whether or not they undergo lavage, is needed to determine whether pulmonary fibrosis results from PAP or is coincidental.

**ACKNOWLEDGMENT:** We thank Dr. Robin T. Vollmer for performing the postmortem examination.

**REFERENCES**