Pulmonary alveolar microlithiasis

M. R. Sears, A. R. Chang, and A. J. Taylor

Departments of Medicine and Pathology, University of Otago Medical School, Dunedin, New Zealand

Pulmonary alveolar microlithiasis is a rare condition of unknown aetiology which is emerging from obscurity and being more frequently recognized. The case histories of two patients, one of whom is the oldest reported case in the literature, are described. In one case extensive fibrosis of interstitial tissue was present and many calcospherites appeared to lie outside the alveolar spaces. Calcospherites were also found in the bronchial wall of this patient, and this has not previously been reported. The lungs were analysed for calcium, phosphate, and iron, and detailed respiratory function tests were done in one patient; all results were similar to those previously reported in this condition.

The first account of pulmonary alveolar microlithiasis is generally attributed to Harbitz (1918) though Friedreich (1856a, b) described several forms of concentrically laminated bodies found in lung parenchyma and suggested that these bodies might be formed within the alveoli. Puhr (1933) suggested that the disease be called 'pulmonary alveolar microlithiasis'. Although Harbitz described the round or oval lamellated concretions as lying in the interalveolar tissue of the lung, with encroachment on the alveolar spaces, further study showed that the calcification producing the typical radiological pattern and functional abnormalities was intra-alveolar, and that the inter-alveolar tissue generally underwent only a minor fibrotic reaction.

Over 90 cases of this rare disease of unknown aetiology have now been reported, the patients falling into all age groups from premature infants of 29 weeks gestation (Caffrey and Altman, 1965) to the ninth decade (present paper), the majority being detected in the fourth to sixth decades. The apparent confinement of the disease to the alveoli has been one factor lending weight to the unproved hypothesis that pulmonary alveolar microlithiasis results from precipitation of calcium at the alveolar interface, in the presence of undue alkalinity possibly caused by an inborn error of metabolism. However, in one of the two cases reported here there was involvement of non-alveolar tissue, namely the bronchial wall, and this cannot be explained by present theories of aetiology.

CASE REPORTS

Case 1 C.S., aged 44 years at the time of his death in 1963, was found to have an abnormal chest radio-
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FIG. 1. Case 1. Chest radiograph showing pulmonary alveolar microlithiasis with apical emphysema and bilateral small pneumothoraces.

laminated calcospherites were present with only slight fibrosis of the alveolar walls (Fig. 2a, b). Right ventricular hypertrophy was the only other abnormal finding, with a right ventricular wall thickness of 6 mm (3 mm being an upper limit of normal). The histological appearances were characteristic with hypertrophied muscle fibres and enlarged plump nuclei.

The lungs were fixed in formalin and later analysed by the following technique:

Duplicate weighed portions of lung tissue were dried to constant weight and then wetashed using nitric and perchloric acids. The iron content of the acid digest was estimated on the atomic absorption spectrometer and the phosphate content by the method of Fiske and Subbarow (1925). The digest was then diluted in 0.5% strontium chloride and calcium content was estimated on the atomic absorption spectrometer. The results were: calcium 24.5% (normal lung 0.08%); phosphate 9.1% (normal lung 0.55%); and iron 0.07% (all expressed as dry weight).

CASE 2 Mrs. A.G., aged 80 at the time of her death, first had a chest radiograph in 1954 after complaining of transient right subscapular pain. She had no symptoms until 1962 when she developed episodic cough with mucopurulent sputum and noted some dyspnoea on moderate exertion. There were widespread crepitations throughout the lungfields but no evidence of cardiac failure. She was admitted to hospital in 1968 with angina pectoris, atrial fibrillation, and cor pulmonale, as shown by elevations of the jugular venous pressure to 4 cm above the sternal angle, right bilateral pitting ankle oedema, hepatomegaly to 2 cm below the right costal margin, a 4th heart sound, and ECG evidence of right axis deviation and increased right ventricular voltage. Despite control of her cardiac failure with digoxin and diuretics, dyspnoea increased and was later present at rest. Prednisone was given for recurrent bronchitis with only temporary improvement. She was readmitted to hospital in January 1970 in severe cor pulmonale with arterial hypoxaemia. Despite treatment, she deteriorated and died on 13 March 1970 after a massive pulmonary embolism.

Radiology The 1954 chest radiograph was reported as normal, but in retrospect soft fine miliary shadows were apparent, particularly in the right upper zone. By 1961 this had progressed only a little, but in 1970
Fig. 2. Case 1. Lung histology, showing intra-alveolar calcifications and slight fibrosis of alveolar wall (a) × 118; (b) × 306.
FIG. 3. Case 2. Chest radiograph showing cardiomegaly and calcific shadowing, particularly in the right upper zone.

the shadowing was more generalized with some areas suggesting fibrosis, and the heart was enlarged (Fig. 3). The calcific density of the shadowing was more apparent in the right lungfield (Fig. 4). Functional assessment is listed in the Table. The vital capacity was reduced but did not change over one year, whereas the total lung capacity, initially normal, showed a moderate decrease. There was no significant airway obstruction. Carbon monoxide (CO) transfer was progressively reduced when measured by the fractional CO uptake method (Bates, 1952), and the steady state (SS) (Filley, MacIntosh, and Wright, 1954) and single breath (SB) (Ogilvie, Forster, Blakemore, and Morton, 1957) methods also gave grossly abnormal results. Not surprisingly, arterial oxygen tension was low and fell further over the course of the last year.

Calcium metabolism was normal, duplicate measurements revealing normal serum calcium (10.5, 10.4 mg/100 ml) serum phosphate (2.8, 3.1 mg/100 ml), and urinary calcium (116, 116 mg/24 hr) levels.

Necropsy The gross findings were very similar to those described in case 1; the hard heavy lungs were difficult to cut and felt like sandpaper. In addition several fine pale-yellow sand-like grains were seen in the mucosa of the main bronchi, particularly about the bifurcation of the trachea, similar in appearance to the sand-like grains seen on the cut surface of the lung. Histologically numerous laminated calcospherites, similar to those in Case 1, were seen in the lung (Fig. 5). A feature was that although many of the calcified bodies were present in alveolar spaces, some appeared to be in septal walls which were greatly fibrosed. The size of some alveoli was reduced as a result of the fibrosis. Few inflammatory cells were seen. Vessels in the interstitial spaces were congested whilst erythrocytes had been extravasated into both alveoli and alveolar walls. Scattered haemosiderin-laden macrophages were also seen.

TABLE

Pulmonary alveolar microlithiasis

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<thead>
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<th></th>
<th>Predicted</th>
<th>May 1969</th>
<th>March 1970</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (litres)</td>
<td>2.33</td>
<td>1.92</td>
<td>1.90</td>
</tr>
<tr>
<td>FEV₁ (litres)</td>
<td>1.79</td>
<td>1.48</td>
<td>1.41</td>
</tr>
<tr>
<td>TLC (litres)</td>
<td>4.11</td>
<td>4.03</td>
<td>3.49</td>
</tr>
<tr>
<td>Fract. CO uptake</td>
<td>35%</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>DLcoSS (rest) (ml/min/mmHg)</td>
<td>8.9</td>
<td>2.6</td>
<td>—</td>
</tr>
<tr>
<td>DLcoSB (rest) (ml/min/mmHg)</td>
<td>19.5</td>
<td>—</td>
<td>4.5</td>
</tr>
<tr>
<td>PacO₂ mmHg</td>
<td>90</td>
<td>64</td>
<td>50</td>
</tr>
</tbody>
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3G
The bronchial nodules contained typical laminated calcospherites lying in groups between the mucosa and the muscular layer of the bronchus (Figs 6 and 7). These were identical with the calcospherites seen in the lung tissue, apart from some fragmentation due to difficulty in sectioning the tissue.

Analysis of the lung tissue by the technique already described gave results similar to those of the first case: calcium 18.3%, phosphate 6.3%, and iron 0.15% dry weight. Technical difficulties precluded analysis of the calcospherites present in the bronchial mucosa.

**DISCUSSION**

Although showing most of the histological features of case 1 and hence the classical features of pulmonary alveolar microlithiasis, case 2 had two unusual histological features.

Firstly, some of the calcospherites appeared to be within thickened alveolar walls. It cannot be entirely excluded, however, that the microliths did not in fact originate in alveoli which later became obliterated and disorganized by the septal fibrosis. Calcification within alveolar septa in a case of pulmonary alveolar microlithiasis associated with the milk-alkali syndrome has been described by Portnoy, Amadeo, and Hennigar (1964). They also noted some microliths embedded in an eosinophilic partially collagenized substance resembling an unresorbed, slightly organized exudate, though most were within distended alveolar spaces. A recent report from Japan (Hotchi, Nasu, and Mihara, 1970) drew attention to the presence of nodules in, and thickening of, the alveolar septa, in a case of pulmonary alveolar microlithiasis. Van Gieson elastic staining was reputed as showing the homogeneous nodules to consist largely of elastic fibre and elastoid tissue, but calcification was not mentioned and appears not to have been present in the nodules. The elastoid tissue appeared identical with that surrounding the ground substance of the microliths. Hence a possible explanation was that the same material which provides ground substance for microliths in the alveoli may form elastoid tissue if accumulated in tissue spaces and subjected to the action of cellular enzymes. Case 2 then may represent a further stage in development of this aspect of the disease, with calcification of the ground substance and elastoid tissue within tissue spaces to form microliths. The word 'elastoid' is taken as a direct quote from Hotchi et al. (1970).

The results of analysis of the calcospherites in case 2 were very similar to those of case 1, and are in agreement with analyses reported by Sosman, Dodd, Jones, and Pillmore (1957), Sharp and Danino (1953), and Hotchi et al. (1970), confirming the calcified bodies of case 2 to be 'alveolar microliths' despite the unusual histological features.

The second feature, not previously reported, is the occurrence of apparently identical laminated calcified bodies within the bronchial wall. Many of the necropsy reports on previous cases do not mention macroscopic or histological examination of the large airways (Caffrey and Altman, 1965; Meyer, Gilbert, and Kent, 1956; Abdel-Hakim, El-Mallah, Hashem, and Abdel-Halim, 1959; Waters, 1960) and in those cases with reports of bronchial examination, the bronchi were normal (Harbizt, 1918; Sharp and Danino, 1953; Sosman et al., 1957; Gomez et al., 1959; Chinachoti and Tangchai, 1957; Hotchi et al., 1970). However, Portnoy et al. (1964), in their patient with the milk-alkali syndrome, hypercalcaemia, and renal lithiasis as well as pulmonary alveolar microlithiasis, found evidence of slight calcification of the bronchial mucous membrane.

The intramural nature of the bronchial involvement must be differentiated from intraluminal concretions occasionally found at necropsy (Portnoy et al., 1964; Hotchi et al., 1970) which
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FIG. 5. Case 2. Lung histology showing calcospherites within alveolar spaces and septal walls (×260).

represent microliths formed in the alveoli and coughed up into the larger airways. There was no evidence from the present case that the intramural bronchial microliths had been initially alveolar in origin, coughed up and trapped in the bronchi to become incorporated into the wall, nor that the bronchial microliths could be extruded into the bronchial lumen. The localized 'clusters' of microliths would argue against the former postulate, and the intact bronchial mucous membrane makes the latter unlikely.

The inhalation of snuff has been a feature in some cases of microlithiasis (Chinachoti and Tangchai, 1957) and the aetiological importance of this is debated. However, in neither of the cases here reported was a history of snuff-taking obtained, nor was there any evidence of mitral stenosis with which pulmonary alveolar microlithiasis has also been associated (Sharp and Danino, 1953). Likewise, there was no familial occurrence of the disease in either case.

Spontaneous pneumothoraces have been reported in a number of other cases of this disease (Waters, 1960) and the development of emphysema is common.

The functional changes found in case 2 are very similar to those reported by Finkbiner, Decker, and Cooper (1957), Thomson (1957), Viswanathan (1962), and Fuleihan, Abbond, Balikian, and Nucho (1969), and are those expected from the nature of the pathological changes found. The deterioration over the last year is likely to be due to progressive fibrosis with maldistribution of ventilation and blood flow, rather than to the increased calcification alone.

The age of the patient, or duration of the disease, might be expected to affect the extent of involvement (Sosman et al., 1957), although the fully developed disease has been found in premature infants with concomitant hyaline membrane disease (Caffrey and Altman, 1965). Our second patient, who at 80 years is probably the
FIG. 6. Case 2. Bronchial histology showing location of microliths between the mucosa and muscular layers (×118).

FIG. 7. Case 2. Bronchial histology showing fragmented lamellated nature of microliths (×210).
oldest reported case of pulmonary microlithiasis, had had radiological abnormalities over a 16-year period. If, as suggested by Sosman et al. (1957), Caffrey and Altman (1965), Balikian, Fuleihan, and Nucho (1968) and others, pulmonary alveolar microlithiasis is genetically determined and is due to an inborn error of metabolism, then the older patients could be expected to show the more marked pathological changes. However, the degree of calcification in this case was less than in many of the cases reported in younger age groups, suggesting differing rates of progression of the disease. Although it is difficult to relate bronchial involvement to age, the greater fibrotic reaction in the interalveolar tissue may reflect the long duration of a relatively indolent form of microlithiasis.

Coetzee (1970) has noted the occurrence of typical calcospherites in the lumbar sympathetic chain, and probably also within the testes, of a patient with pulmonary alveolar microlithiasis, providing support for postulating a systemic or metabolic derangement as an aetiological factor.

From the two cases presented, no evidence is forthcoming as to aetiology, but whatever this might be, pulmonary microlithiasis must no longer be regarded as confined to the alveoli, and in each case a careful search should be made for other sites of involvement which may help in elucidating the nature of this fascinating disease.

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