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PULMONARY ALVEOLAR MICROLITHIASIS

BY

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Pulmonary alveolar microlithiasis is a rare condition in which intra-alveolar, calcified, laminated concretions occur throughout the lungs in the absence of any known disturbance of calcium metabolism. This type of extensive calcification within the lungs was first described by Harbitz (1918). The name "mikrolithiasis alveolaris pulmonum" was suggested first by Puhr (1933).

Sosman, Dodd, Jones, and Pillmore (1957) have recently reviewed the literature on 22 previously reported cases (20 proved, two probable) and have described 23 new ones emphasizing the familial occurrence of the condition. Since their report further cases have been described by Gilsanz, Palacios, and Alonso Barrera (1956), Biressi and Casassa (1956), Finkbiner, Decker, and Cooper (1957), Greenberg (1957), and Chinachoti and Tangchai (1957). The last report, which comes from Thailand, is interesting because it describes the occurrence of pulmonary microlithiasis (confirmed by necropsy) in a man who had been addicted for 23 years to the daily inhalation of about 7.5 g. of a Siamese snuff containing approximately 9.5% calcium and only 1.6% silica. The authors state that they have seen eight other snuff addicts with abnormal routine chest radiographs, but do not indicate the nature of the abnormalities. Good accounts of the morbid anatomy and discussions of the aetiology of pulmonary microlithiasis may be found in the reports of Sharp and Danino (1953), Kent, Gilbert, and Meyer (1955), and Sosman and others (1957).

This paper reports a case of pulmonary alveolar microlithiasis, thought to be the third reported from the British Isles, although two other patients who are brothers are known to have the disease (Doig, 1957, personal communication). A full assessment of pulmonary function has been made in the present case. Extensive function studies in this disease have previously been reported only by Finkbiner and others (1957) in one case.

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CASE REPORT

The patient was aged 34 years when first seen in April, 1956. He had been a coal-miner for most of his life, but apart from childhood illnesses and an episode of dyspepsia in 1941, said to be due to a peptic ulcer, he had remained well until January, 1956, when he developed an occasional dry cough. In March, 1956, he experienced a sudden, severe pain in the front of the chest which was worse on breathing and associated with some dyspnoea. The pain ceased after 10 minutes and he completed his shift at the coalface. After this he admitted to slight dyspnoea on severe exertion. He was referred because of the unusual appearances of his chest radiograph taken at that time. No previous radiographs were available.

On examination he looked well with no apparent breathlessness or cyanosis. There was gross clubbing of the fingers and moderate clubbing of the toes; his peculiar finger nails had been noted at school by other children. The chest expansion was 1¼ in. (3 cm.). Medium-fine rales were audible over the lower parts of both lungs, back and front. There was no other physical abnormality.

The patient's family was extensively investigated by the M.R.C. Pneumoconiosis Research Unit, Cardiff, but no other case of pulmonary microlithiasis was found. The survey included 60 persons of whom only four were not traced. The patient's mother and the majority of her family, two of his three brothers, and his three children were all radiographed with negative results. There was no record of any chest radiographs of his three paternal uncles and one paternal aunt, nor of his father, who died aged 34 from septicaemia.†

The following laboratory investigations were performed: haemoglobin, 18 g./100 ml.; P.C.V., 53%; leucocytes, 9,000/c.mm.; E.S.R., 3 mm. in one hour (Westergren); serum calcium 10.2 mg., phosphate 4.0 mg., protein 8.0 g. per 100 ml. (albumin 3.1 g., globulin 4.9 g.); alkaline phosphatase 11.9 King-Armstrong units; 24-hour urinary calcium excretion 224 mg.; chest radiographs showed widespread mottling of a calcific density obscuring the mediastinal shadows and nearly the whole of both lung fields. An over-penetrated view showed some increased density in the sub-apical zones on both

†Details of the family survey in this case may be obtained from the M.R.C. Pneumoconiosis Research Unit, Llandough Hospital, Cardiff.

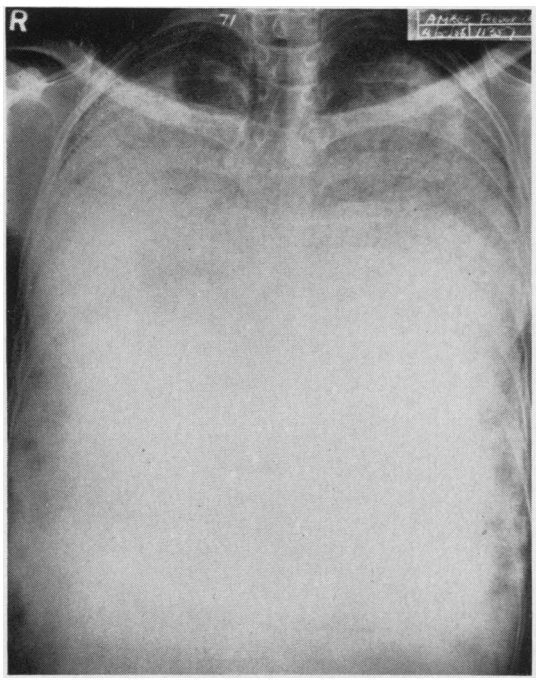

FIG. 1.—Chest radiograph by standard technique.

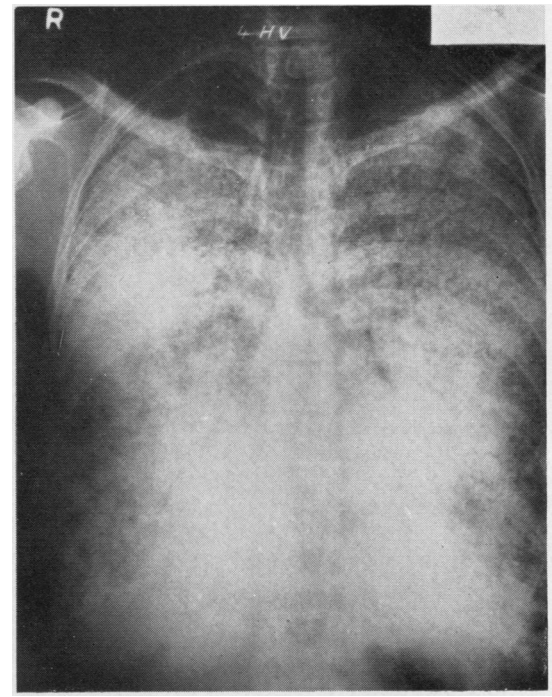

FIG. 2.—Overpenetrated chest radiograph.

sides and a normal bronchial architecture (Figs. 1 and 2). Results of pulmonary function tests are shown in Table I.

DISCUSSION

DIAGNOSIS AND CLINICAL PICTURE. — The majority of reported cases (32 out of 50) have been diagnosed, like this one, as a result of routine chest radiography for some incidental complaint. Although lung biopsy has been performed in some cases this is quite unnecessary when the condition is fully developed. No other pulmonary disease produces miliary calcification in the lung of such density, and once recognized it can be diagnosed with confidence from a single radiograph. Rarely the calcification is less intense (Sosman and others, 1957) when differentiation from other causes of disseminated miliary calcification may be more difficult.

Although the radiological changes may have been well described (Sosman and others, 1957) the clinical features are not so clear. The diagnosis has usually been made in early adult life, but with the more frequent use of mass radiography and the appreciation of the familial occurrence of the condition, more examples are being found in children (Sato, 1955; Sosman and others, 1957; Greenberg, 1957), the youngest so far reported being 6 years old. Because it is so uncommon and so few cases have been followed for a long time the course of the disease is uncertain, but usually there appears to be a slow progression over many years. Thus the patient described by Manz (1954) had the disease for at least 25 years before she died in congestive cardiac failure at the age of 37 years. On the other hand, the case reported by Biressi and Casassa (1956) is of interest because a chest radiograph in 1946 was said to be clear, but by 1947 there was dense shadowing obscuring both lung fields; this is so unlike the course of other reported cases that it is permissible to speculate on the possibility of mistaken identity. The patient died in 1955, eight years after the apparent onset, also of congestive cardiac failure. The oldest proven patient was 66 years old at death (from congestive heart failure) although it is possible that a 72-year-old man reported by Bénard, Rambert, Péquignot, Tissier, and Galistin (1950) also had the condition. Nine of 16 recorded deaths (at ages 28 to 66) have been from cardiac failure, presumably due to pulmonary heart disease.

The symptoms and signs vary with the stage in the disease at which the patient is seen, the onset of cardiac failure tending to obscure symptoms and signs due to the underlying pulmonary lesion. Before this stage is reached symptoms are either

absent or very mild, consisting usually of dyspnoea on severe exertion only. Cough does not appear to be a conspicuous feature in the majority of patients. The contrast between the minimal symptoms and the gross radiological changes, which is well shown by our patient, has been noted by many previous authors (Lindig, 1951; Sharp and Danino, 1953; Meyer, Gilbert, and Kent, 1956; Sosman and others, 1957; Finkbiner and others, 1957) and is characteristic of the condition in its early stages.

The relationship between the physical signs and the pathological changes in the lungs is difficult to assess. Finger clubbing has been described in 11 of the 50 cases reported up until December, 1957, but in many cases no specific reference is made to the fingers. In four of these patients the clubbing was associated with cyanosis and possibly heart failure, but this was apparently not the case in the other seven. Our patient's fingers had been noted to be peculiar while he was still at school, and thus antedated his respiratory symptoms. The possibility that it might be familial was considered, but the three other members of his family seen had normal fingers.

The other striking physical sign in this patient was the numerous medium-fine rales easily heard over the anterior, lateral, and posterior aspects of the lower chest on both sides. Rales over the lower chest in the absence of heart failure have been noted in 12 of the 50 previously reported cases (again inadequacy of many reports suggests that this is a low estimate of the frequency of this sign). Pulmonary rales were noted more frequently in the recent reports where good clinical accounts are included (Badger, Gottlieb, and Gaensler, 1955; Biressi and Casassa, 1956; Sosman and others, 1957; Finkbiner and others, 1957) and they probably result directly from the pulmonary lesion.

TABLE I

RESULTS OF PULMONARY FUNCTION TESTS

Subject: Male, Age 35 Years Ht. 174 cm.: Wt. 50·9 kg.	May, 1956	Sept., 1956	April, 1957	Normal Values
Lung volumes (litres B.T.P.S.):				Range
Vital capacity	2·67	2·51	2·68	3·6–5·4
Inspiratory capacity	1·67	1·69	—	3·1–3·5
Expiratory reserve volume	1·00	0·82	—	0·8–1·9
Functional residual capacity	2·97	3·01	—	2·6–4·8
Residual volume	1·97	2·19	—	1·5–3·0
Total lung capacity	4·64	4·70	—	5·7–8·3
RV/TLC%	45·2%	46·6%	—	23–41
Ventilation (sitting):				
Tidal volume (litres)	0·49	—	—	Approx. 0·6
Respiratory rate (breaths per min.)	20	—	—	,, 15
Minute volume (litres/min.)	9·80	—	—	,, 9
Respiratory dead space (assumed) (ml.)	150	—	—	
Alveolar ventilation (litres/min.)	6·80	—	—	,, 6
Distribution of inspired gas:				
Mixing efficiency (helium: closed circuit method)	36·0%	36·5%	—	61–94 (77·4%)
Unevenness of distribution of inspired gas (single breath method)	—	—	30%	<7%
Alveolar ventilation: pulmonary blood flow ratios:				
Unevenness of distribution of ventilation: perfusion ratios (single breath method)	—	—	14%	<5%

TABLE I—*continued*

Subject: Male, Age 35 Years Ht. 174 cm.: Wt. 50·9 kg.	May, 1956	Sept. 1956	April, 1957	Normal Values
Pulmonary circulation:				
Unevenness of distribution of pulmonary blood flow (single breath method)	—	—	25%	<6%
Gas diffusion:				
Diffusing capacity carbon monoxide (ml. CO/min./mm. Hg)				
Rest	5·8	4·2	—	10–30 approx.
Exercise (2½ m.p.h. on flat)	8·1	6·5	—	21–44 approx.
Mechanics of breathing:				
Forced expiratory volume (1 sec.) ($FEV_{1·0}$) litres	2·16	2·17	2·04	2·83–4·89
Maximum breathing capacity (calculated from FEV) litres/min.	74	76	70	99–171
$FEV_{1·0}$/VC ratio (×100)	81%	81%	79%	>70%
Lung compliance (litres/cm. H_2O)	0·071	0·057	—	0·120–0·200
Airway resistance (cm. H_2O/litre/sec.)	2·21	—	—	1·5–2·5
Standardized exercise test (350 kg./m. for 5 min.):				
Standardized ventilation (litres/min.)	38·5	34	40	20–37
Exercise ventilation (litres/min.)	38·0	32	39	
Dyspnoeic index (SV/MBC ×100)	59%	51%	58%	<30%
Ear oximetry:				
Rest	—	—	89%	>96%
Exercise (5 min.)	—	—	55%	>96%
Rest	—	—	89%	>96%
On 100% oxygen by "polymask"	—	—	97%	100%

Methods: Lung volumes, forced expiratory volume ($FEV_{1·0}$) and indirect maximum breathing capacity ($FEV_{1·0} \times 35$) by simple spirometry. Mixing efficiency by helium closed circuit method (Bates and Christie, 1950), evenness of ventilation, ventilation-blood flow ratios, and pulmonary blood flow by single-breath method using respiratory mass spectrometer (West, Fowler, Hugh-Jones, and O'Donnell, 1957); diffusing capacity by steady-state carbon monoxide method (Bates, 1952; Bates, Boucot, and Dormer, 1955); lung compliance and airways resistance using oesophageal balloon and pneumotachygraph (Mead and Whittenberger, 1953); standardized exercise test (Hugh-Jones and Lambert, 1952).

The normal ranges for the lung volumes, maximum breathing capacity, and mixing efficiency are taken from Needham, Rogan, and McDonald (1954); otherwise they were taken from the papers cited above.

PULMONARY FUNCTION STUDIES. — Some assessment of pulmonary function in pulmonary alveolar microlithiasis has been made in 22 of the 50 previously reported patients, but in 14 this consisted only of a measurement of the vital capacity. Studies in the other eight cases were more detailed, the most comprehensive being those reported in one case by Finkbiner and others (1957). The main functional abnormalities noted by these authors were a restriction of the total and vital capacities, unevenness of distribution of inspired gas, impaired gas diffusion, and a reduced lung compliance. The maximum breathing capacity was, however, normal. Their patient was a 33 - year - old Negro with pulmonary microlithiasis of a similar order of severity to the patient reported here, in that he had virtually no respiratory symptoms but marked radiological changes and there was no evidence of cardiac failure. Comparisons of the type and degree of functional change in the two patients are therefore interesting.

The disturbances of pulmonary function found in our patient can be considered under the following headings: (1) Reduced vital and total lung capacities ; (2) reduced maximum breathing capacity ; (3) uneven distribution of inspired gas ; (4) uneven distribution of ventilation/blood flow ratios ; (5) uneven distribution of pulmonary blood flow ; (6) reduced diffusing capacity ; and (7) reduced lung compliance.

The vital capacity was reduced in 19 of the 22 previously reported patients in whom it was measured. The reduction of the vital and total lung capacities, in both this patient and that of Finkbiner and others, was due mainly to a limitation of the inspiratory capacity indicating the presence of a " restrictive " type of ventilatory defect which is commonly found in pulmonary fibrosis from any cause. These results are compatible with the finding of fibrosis and thickening of the alveolar wall on microscopy (Sharp and Danino, 1953 ; Kent and others, 1955 ; Sosman and others, 1957 ; Finkbiner and others, 1957). The vital capacity is not sufficiently reduced to prevent a pulmonary ventilation adequate for most ordinary activities.

The maximum breathing capacity (M.B.C.) has been measured in eight of the previously reported patients. It was reduced in five but normal in the other three, one of which was the patient reported by Finkbiner and others (1957). In the patient described here the M.B.C. was reduced to about three-quarters of the lower limit of normal for his age, but this is still sufficient for all but the most strenuous exertion.

The abnormal increase in the ventilatory response to standard exercise (Hugh-Jones and Lambert, 1952) was probably due to the impairment of gas diffusion and to the disturbances in the distribution of inspired gas and pulmonary blood flow.

Uneven distribution of inspired gas was reported by Sosman and others (1957) and by Finkbiner and others (1957), but uneven ventilation-blood flow ratios throughout the lung and uneven pulmonary blood flow have not been demonstrated in pulmonary microlithiasis before. There is adequate cause for these disturbances on morbid anatomical grounds, for in addition to the intra-alveolar concretions which themselves probably interfere with the distribution of inspired gas, obliteration of pulmonary capillaries and areas of localized emphysema have both been reported (Sharp and Danino, 1953 ; Kent and others, 1955 ; Biressi and Casassa, 1956 ; Sosman and others, 1957 ; Finkbiner and others, 1957).

Apart from the microliths themselves, an important histological feature in some cases is thickening of the alveolar walls (Badger and others, 1955 ; Sosman and others, 1957). There is also evidence that the microliths are adherent to the alveolar walls in many parts of the lungs (Sharp and Danino, 1953). These lesions might impair gas diffusion across the alveolar membrane. A diffusion defect was suspected, on the basis of an increased alveolar-arterial oxygen gradient, by Badger and others (1955). In both the patient reported here and in that reported by Finkbiner and others (1957) there was impaired uptake of carbon monoxide. Finkbiner and others did not indicate how they measured carbon monoxide uptake, but in the present case the " steady state " method (Bates, 1952 ; Bates, Boucot, and Dormer, 1955) was used. Normally, by this method, the carbon monoxide uptake rises from a resting value of approximately 10 to 30 ml. CO/min./mm. Hg to 21 to 44 ml./min./mm. Hg on moderate exercise (Bates and others, 1955). In our patient not only was the resting value reduced (5 ml. CO/min./mm. Hg) but the usual increase on exercise was much less than normal, so that on moderate exercise ($2\frac{1}{2}$ m.p.h. on the flat) the uptake (8 ml. CO/min./mm. Hg) was still below the normal resting level. In the steady state method the uptake of carbon monoxide is as much affected by uneven distribution of inspired gas as by impairment of gas diffusion (Marshall, 1958). However, the fall in arterial blood oxygen saturation found by ear-oximetry during the standardized exercise test suggests a considerable diffusion defect. Oxygen desaturation at rest and

on exercise was also found by Finkbiner and others (1957) using direct arterial puncture.

Reduction of lung compliance is another finding common to this patient and that of Finkbiner and others. It is frequent in pulmonary fibrosis from any cause, and may contribute to dyspnoea by increasing the work of breathing.

The arterial blood gas tensions and *p*H were not measured, so that it is not known whether the patient had the acidosis found by Finkbiner and others (1957). Otherwise the findings in the two patients agree remarkably well. It seems that patients with pulmonary microlithiasis may have quite mild symptoms despite well-developed radiological changes and laboratory evidences of disturbed pulmonary function.

In summary, the pulmonary function tests indicate that in this patient ventilation of the lungs as judged by the M.B.C. is surprisingly good in view of the gross radiological changes. However, reduction in the diffusing capacity and the disturbance of ventilation perfusion ratios cause hypoxia, which may become severe on exertion.

MANAGEMENT.—Since the cause of pulmonary alveolar microlithiasis remains unknown there is no specific remedy. However, from a knowledge of the morbid anatomical and functional changes, suggestions for management can be made. The available histological evidence suggests that the microliths probably result from calcification in an intra-alveolar exudate derived from the alveolar capillaries (Sosman and others, 1957). The mononuclear and giant cell infiltration of the alveolar walls noted on microscopy in some cases (Leicher, 1949 ; Manz, 1954 ; Badger and others, 1955 ; Sosman and others, 1957) probably arises as a reaction to the concretions, but could possibly be part of a primary inflammatory process. In either case, the inflammatory changes in the alveolar wall probably contribute, with the fibrosis, to the reduction in the diffusing capacity. The existing concretions and the fibrotic changes cannot be resolved, but it does seem worth while attempting to arrest or reduce either the inflammatory changes in the alveolar wall or the production of an intra-alveolar exudate. The obvious agents for use in this respect are the steroid drugs. Badger and others (1955) used corticotrophin and later cortisone on their patients, but considered, on clinical grounds, that neither drug altered the progress of the disease.

An attempt was made to assess the value of cortisone in the patient reported here by performing pulmonary function tests before and during its use as well as by clinical observation. Unfortunately, as the patient would not remain in hospital and close out-patient supervision could not be arranged the dose of cortisone was restricted. An initial dose of 300 mg. during the first day was gradually reduced over the following week to a maintenance dose of 50 mg. daily. This was continued for approximately three months from June to September, 1956, when respiratory function tests were repeated. This treatment produced no symptomatic improvement, and Table I shows that there was no change in the results of the pulmonary function tests.

The major functional disturbance from the point of view of management is the hypoxia which was present at rest and which became severe on exercise. Hypoxia, if severe or persistent, can lead to progressive damage in many body tissues (Simpson, 1957). It may be an important factor, together with the obliterative changes in the smaller pulmonary blood vessels (Sharp and Danino, 1953 ; Finkbiner and others, 1957) in the production of pulmonary heart disease (Wood, 1956). Nine of the 15 reported deaths in the condition have been due to heart failure. The increased hypoxia on exertion could be avoided by continuous oxygen administration with a portable apparatus (Cotes and Gilson, 1956). This was impracticable in our patient, but he was advised against any occupation or activity involving strenuous exercise.

Finally, there is the question of respiratory infections in these patients. They do not appear to be especially susceptible to infections, but many of the terminal episodes of cardiac failure appear to have been precipitated by a respiratory infection. Such infections may lead to respiratory failure in subjects with impaired pulmonary function. It is suggested, therefore, that these patients should be instructed to seek immediate medical advice at the onset of any upper respiratory symptoms.

SUMMARY

A case of pulmonary alveolar microlithiasis studied by lung function tests is reported and the course, clinical features, and management discussed.

The diagnosis was made on clinical and radiological grounds without recourse to lung biopsy.

Pulmonary function studies indicated that impairment of gas diffusion across the alveolar membrane, and uneven relative distribution of gas and blood in the lungs, were the most important

disorders of pulmonary function in this patient. They may lead to serious hypoxia on exertion. There was also a mild "restrictive" type of ventilatory defect and a reduced lung compliance.

In the management of patients with this condition hypoxia may be limited by the avoidance of strenuous exertion.

Cortisone, 50 mg. daily for three months, produced no apparent improvement in pulmonary function.

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