

Asbestos induced diffuse pleural fibrosis: pathology and mineralogy

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ABSTRACT Lungs from seven cases of diffuse pleural fibrosis with known asbestos exposure were studied to determine the gross and microscopic pathological features and relate these to the analysed mineral fibre content of the lung. All seven individuals had had substantial exposure, ranging from two to 25 years, and chronic chest problems and at necropsy all cases met the criteria for compensable disease. Macroscopically, all had extensive visceral pleural fibrosis and extensive areas of adhesions, and four also had discrete parietal pleural plaques. The histological features were similar in all the cases—most strikingly the basket weave pattern of the thickened pleura and a dense subpleural parenchymal interstitial fibrosis with fine honeycombing, extending up to 1 cm into the underlying lung. The similar histological appearances raise the possibility that diffuse pleural fibrosis and pleural plaques have a similar pathogenesis. Amphibole asbestos (crocidolite and amosite) counts were high in six of the seven cases and chrysotile counts in four; four cases had high mullite counts, but the importance of this is not known. It is concluded that diffuse pleural fibrosis is a specific asbestos associated entity, of uncertain pathogenesis, with mineral fibre counts falling between those found with plaques and those in minimal asbestosis.

Introduction

Diffuse pleural fibrosis is a well recognised component of asbestos induced parenchymal disease,¹ but only more recently has it become accepted as a specific entity in its own right.² Some clinico-radiological reports have appeared, but the underlying pathological changes remain poorly documented and no mineralogical data are at present available. In this paper we describe the gross and microscopic features of the condition and discuss the relationship with the analysed pulmonary mineral fibre content.

Methods

Lungs were examined from necropsies performed from 1979 to 1986 on seven cases of known asbestos exposure. They were drawn from about 1200 asbestos related necropsies. Clinical and occupational histories

were obtained from hospital notes or from the Pneumoconiosis Medical Panel. Causes of death were obtained from death certificates.

TISSUE PREPARATION

Lungs were distended by formalin in the standard manner and examined macroscopically after fixation. Blocks of tissue were taken from the apex of the upper lobe, the apex of the lower lobe, and the base of the lower lobe. In addition, several blocks were taken from the visceral pleural surface. The centre of each of the parenchymal blocks was taken for histological examination and the remainder submitted for mineralogical analysis.

Paraffin sections were prepared and stained by haematoxylin and eosin; Martius scarlet blue was used for fibrous tissue, and elastic-Van Gieson's method for elastic and fibrous tissue. The degree of parenchymal fibrosis was graded from 0 to 4 by an established system for each histological slide and an average was obtained for each case.^{3,4}

MINERAL FIBRE ANALYSIS

Both light microscopic and electron microscopic counts were undertaken. The light microscopic

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Table 1 Diffuse pleural fibrosis: clinical and occupational features

Case No	Age (y)	Occupation	Clinical features
1	80	Pipe fitter (25 y asbestos exposure)	Severe dyspnoea and wheeze for 10 years; chronic obstructive airways disease; coexistent restrictive ventilatory defect; smoker (20/day for 50 y)
2	75	Electrical welder	Chronic chest disease with recurrent chest infections for several years; smoked 20/day for several years
3	67	Engineer (2 y exposure cutting asbestos sheets 40 y ago)	"Chronic chest disease" for 4 years
4	69	Maintenance fitter (2 y exposure 20 y ago)	Productive cough for several years; smoked 50/day for several years
5	58	Caravan maker—blue asbestos (9 y exposure 15 y ago)	Recurrent pleural effusions for 2 y; normal lung function test results 7 y before death; smoked 20/day for several years
6	68	Munitions factory worker	Recurrent bilateral pleural effusions for 4 y; recurrent chest infections; smoked 20/day for several years
7	64	Ex-boilermaker (heavy exposure)	"Obstructive airways disease" for 7 y; bilateral pleural thickening noted radiologically 7 y before death; smoked 20/day for several years

counts were performed by the method of Ashcroft.⁵ Briefly, lung tissue was divided into two portions and weighed, one half being dried and reweighed and the other digested by immersion in sodium hydroxide. After centrifugation the supernatant was aspirated and the sediment resuspended in water. An aliquot was then transferred to a Fuchs-Rosenthal chamber and fibres were counted by phase contrast microscopy. The count was related to the dry weight of the lung tissue. Electron microscopic counts were per-

formed as a standard procedure.⁶ Tissue samples were dried at 80°C, digested in sodium hydroxide, washed, and ashed in an oxygen atmosphere. The final extract was suspended and filtered on to a nucleopore filter. The filter preparation, laden with dust from a known weight of dried tissue, was coated with carbon, the filter dissolved with chloroform, and the carbon film mounted on to a gold electron microscope support grid. The electron microscopic preparations were examined and all fibrous particles counted, the figures obtained being related to the original dry weight of the lung tissue. Then 100–200 fibres were analysed by an energy dispersive x ray analysis technique.⁷

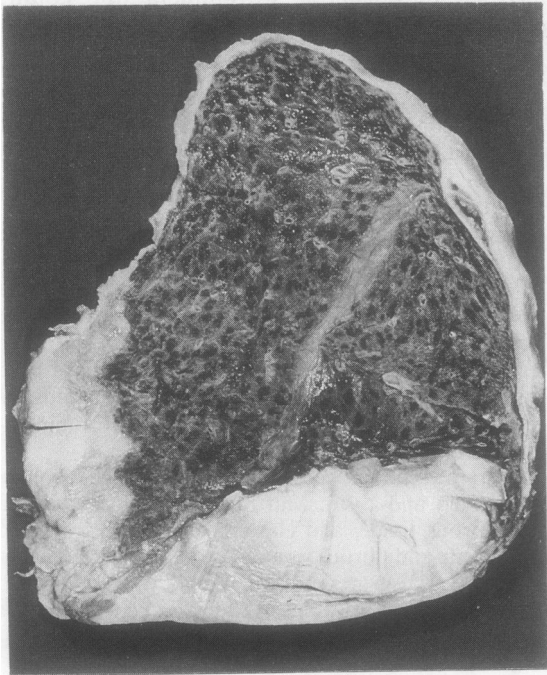


Fig 1 The lung from case 2, showing complete encasement by diffuse pleural thickening. The under surface is shown in the lower part of the figure.

Results

CLINICAL AND OCCUPATIONAL FINDINGS
All cases were male and had had substantial exposure to various types of asbestos, ranging from two to 25 years (table 1). Clinically, all had had chronic chest problems and in particular two had evidence of recurrent unexplained pleural effusions. Diffuse pleural thickening was observed radiologically before death in cases 1, 4, and 7. Diagnoses of diffuse pleural fibrosis were obtained only after necropsy in cases 1, 3, 5, and 6; plaques had been noted radiologically in case 5, but in none were the radiological changes diffuse pleural fibrosis observed.

PATHOLOGY

Macroscopic findings

In all cases there was extensive visceral pleural fibrosis, most noticeable at the bases but extending over the upper lobes (fig 1). This was bilateral and many areas greater than 5 mm in thickness. It extended over more than half of each lung surface and in two cases covered the whole lung. There were extensive areas of adhesion between the pleura and the chest wall, giving rise to difficulty in removing the

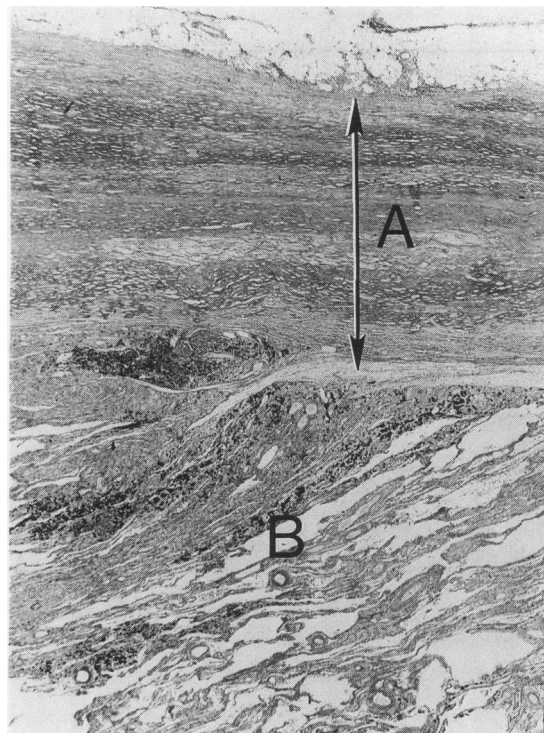


Fig 2 Histological sections from case 2, showing a basket weave pattern of the thickened collagenous pleura (A) with underlying interstitial fibrosis of the lung (B). (Haematoxylin and eosin, $\times 14$.)

lungs from the thoracic cavity at necropsy. In several places, however, the visceral pleura although thickened was smooth with no adhesion to the chest wall. In four cases discrete typical parietal pleural plaques were identified in addition to diffuse pleural fibrosis. No effusions, empyema, or tumour were seen in the pleural space at necropsy. Macroscopic assessment of lung parenchymal fibrosis was made difficult by the presence of lung cancer in three cases and severe pneumonia in three cases.

Microscopic findings

All the cases showed similar histological features. The most striking feature was the basket weave pattern of fibrosis, with preservation of the external elastic laminae and submesothelial fat in many areas of diffuse fibrosis (figs 2 and 3). In other areas there was adhesion of the visceral and parietal layers with obliteration of the pleural space, elastic laminae, and submesothelial fat. Little fibrinous exudate was seen on the pleural surface and no cellular fibroblastic proliferation or organisation was present. In addition, no mesothelial hyperplasia (or neoplasia) was identified.

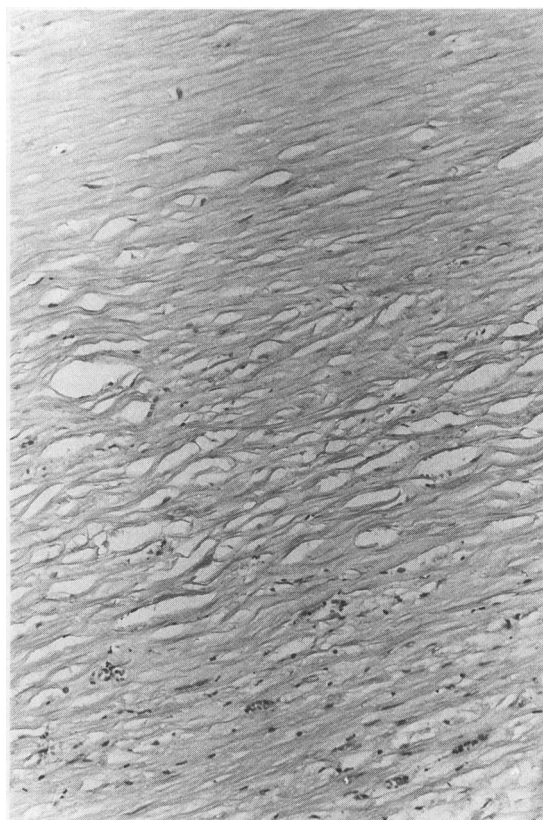


Fig 3 Histological section from case 2 at higher magnification, showing the basket weave pattern of the pleural fibrosis. (Haematoxylin and eosin, $\times 117$.)

In all cases there was dense subpleural parenchymal interstitial fibrosis and fine honeycombing, but this did not extend more than 1 cm into the underlying lung (fig 2). The degree of pulmonary interstitial fibrosis ranged from 1 to 3 (table 2). There was extensive pleural calcification in case 4, but in the others it was inconspicuous.

MINERALOGY

Table 3 shows the asbestos fibre counts by light and electron microscopy. The amphibole (crocidolite and amosite) counts in six cases were high, ranging from 2.4 to $28 \times 10^6/\text{g}$ dried lung. In case 6, however, the amphibole count was relatively low and within our normal range (less than $10^6/\text{g}$ dried lung).

Discussion

Diffuse pleural fibrosis was considered to be an unusual manifestation of asbestos exposure, but

Table 2 Diffuse pleural fibrosis: cause of death and pathological features

Case No	(Age y)	Cause of death	Pathological features
1	80	1a Cor pulmonale 1b Diffuse pleural fibrosis 1c Asbestosis	Grade 2 interstitial fibrosis
2	75	1a Bronchopneumonia 1b Diffuse pleural fibrosis 1c Asbestosis	Grade 2 interstitial fibrosis
3	67	1a Myocardial infarction	Grade 2-3 interstitial fibrosis
4	69	1a Carcinomatosis 1b Carcinoma of lung	Grade 2-3 interstitial fibrosis Adenocarcinoma
5	58	1a Carcinomatosis 1b Carcinoma of lung 2 Asbestosis	Grade 1 interstitial fibrosis Adenocarcinoma
6	68	1a Senile myocardial degeneration 2 Pleural fibrosis	Grade 1 interstitial fibrosis
7	64	1a Pneumonia 2 Carcinoma of lung	Grade 1-2 interstitial fibrosis Large cell carcinoma

Table 3 Mineral fibre analysis in seven cases of diffuse pleural fibrosis

Case No	LM counts per g dried lung	EM counts (10^6 per g dried lung)						
		Total fibre count	Crocidolite	Amosite	Chrysotile	Mullite	Rutile	Other
1	100 000	24.4	0.5	8.3	2.5	12.6	—	Talc 0.5
2	131 027	83.5	10.7	2.9	8.8	60.1	1.0	Iron particles
3	Not done	9.2	1.8	0.7	1.6	4.4	0.3	Muscovite 0.2 Talc 0.2 Actinolite 1.75 Iron oxide 11.5
4	306 000	48.2	5.8	0.9	6.7	21.5	—	—
5	378 000	39	28.08	—	8.9	—	1.95	—
6	Not done	28.9	—	0.5	14.4	9.6	3.4	Silica 0.5 Aluminium 0.5
7	29130	12.5	1.4	1.4	3.5	6.1	0.1	—

EM—electron microscopic; LM—light microscopic.

increasing awareness of this association is reflected in clinical reports of incidence varying from 6% to 36%.⁸⁻¹⁰ All of the cases fulfilled the criteria of compensatable disease—namely, bilateral, over 5 mm thick, and covering more than one quarter of the chest wall.² These diagnostic recommendations are preliminary and clarification of the clinical, radiological, and pathological features will be necessary to understand and define the limits of this condition more carefully.

The pathological changes of diffuse pleural fibrosis were described initially by Gloyne¹¹ and subsequently by Wagner,² but have received scant attention since. There are both similarities and differences between diffuse pleural fibrosis and pleural plaques. The present cases show extensive continuous fibrosis, affecting mainly the visceral pleura; by contrast, plaques tend to be discrete localised lesions confined to the parietal pleura. Another difference is that adhesions between the visceral and parietal pleura are common with diffuse pleural fibrosis but unusual with plaques. Cases of extensive plaque formation are well described but these tend to be discontinuous lesions clearly identified as plaques. A small proportion of plaques, however, have visceral extension and adhesion and can coexist with diffuse pleural fibrosis.

These borderline lesions suggest that there may be a continuum between plaque and diffuse pleural fibrosis. Microscopically there are several similarities including the typical basket weave fibrous structure, focal lymphocytic collections, and scant cellular fibroblastic activity. In diffuse pleural fibrosis, however, there is fusion of the two pleural layers with obliteration of the submesothelial elastic tissue and much of the fatty connective tissue, suggesting that a severe inflammatory reaction has occurred. A notable feature in all these cases of diffuse pleural fibrosis is thin subpleural honeycombing (interstitial fibrosis) without appreciable diffuse parenchymal disease. This change may be explained by pleural drift of the mineral fibres.¹² In none of these cases was evidence of asbestosis detected clinically or radiologically. The degree of pleural fibrosis appeared disproportionate to the parenchymal fibrosis.

The cases presented here are clearly related to occupational exposure to asbestos. It is also apparent that they are associated with both a higher total asbestos count than non-occupationally exposed individuals and a different fibre distribution. In our laboratory non-exposed individuals have light microscopic counts below 20 000/g dried lung and cases with pleural plaques 10 000–50 000/g dried lung.¹³

these cases of diffuse pleural fibrosis clearly exceed this and reach the numbers observed in minimal to slight asbestosis. This is paralleled by the high total electron microscopic counts. Not only are the total electron microscopic counts raised but the numbers of amphiboles are high. In non-occupationally exposed individuals amphiboles were all under $2 \times 10^6/\text{g}$ dried lung,¹³ whereas in six out of seven cases of diffuse pleural fibrosis the values are considerably higher. Churg¹⁴ has also found high levels of amphibole in lungs with pleural plaques.

Four of the cases moreover had high mullite counts; we do not at present know whether this is important. In view of the differences in fibre counts between cases of diffuse pleural fibrosis, plaques, and interstitial fibrosis, investigation of the physical characteristics of the fibres, such as aspect ratio, are required to shed further light on the pathogenesis of the different reactions.

Several conditions can give rise to diffuse pleural fibrosis with obliteration of the pleural space, including trauma, tuberculosis, pleurisy, emphysema, and rheumatoid arthritis.¹⁵ In the present series there was no evidence of any of these conditions. Diffuse pleural fibrosis has long been recognised as a component of severe interstitial fibrosis induced by heavy asbestos exposure,¹³ and more recently as a consequence of asbestos exposure without appreciable pulmonary fibrosis.² Several authors have noticed that diffuse pleural fibrosis can develop within a few months,¹⁶ and that it may be a sequel to benign recurrent pleural effusion associated with asbestos.^{12,15} One third of the cases of McLoud *et al*¹⁰ were associated with previous effusions. In the present series only two out of seven had a history of such effusions, but silent episodes could have occurred in the other cases. The fibrosis is considered by some to result from direct inflammatory damage to the mesothelium with subsequent effusion and healing.¹⁵ The presence of adhesions and obliteration of the external elastic laminae supports this contention but it does not shed any light on whether it is due to recurrent acute episodes or chronic progressive change. The similarity of the histological appearances of diffuse pleural fibrosis and of plaques raises the possibility that the fibrosis is not simply an organised inflammatory exudate but may have a pathogenesis similar to that of plaque formation. The exact mechanism of this is obscure but, in contrast to the pleurisy, direct mesothelial damage is considered not to occur.^{15,17} The subpleural fibrosis noted in these cases indicates that local parenchymal damage had occurred, which may be explained by the pleural drift of fibres. The substantial pleural reaction may be related to the physical nature of the mineral fibres, but individual susceptibility cannot be excluded. Immunological abnormalities have been

described in individuals exposed to asbestos.¹⁸⁻²⁰ Hillerdal²⁰ found that patients with a persistently raised erythrocyte sedimentation rate had radiological evidence of pleurisy or its sequelae, whereas the rate was normal in patients with plaques. He concluded that immunological factors played a part in the pathogenesis of the pleurisy.

In conclusion, diffuse pleural fibrosis is a specific asbestos associated entity. The mineral fibre counts fall between the counts found with plaque formation and with minimal asbestosis. The pathogenesis is uncertain and further work on immunological function and the physical characteristics of the mineral fibres present is required to explain the evolution of this particular reaction.

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