Desquamative interstitial pneumonia associated with chrysotile asbestos fibres

Jeffrey A Freed, Albert Miller, Ronald E Gordon, Alf Fischbein, Jerome Kleinerman, Arthur M Langer

Abstract

The drywall construction trade has in the past been associated with exposure to airborne asbestos fibres. This paper reports a drywall construction worker with 32 years of dust exposure who developed dyspnoea and diminished diffusing capacity, and showed diffuse irregular opacities on chest radiography. He did not respond to treatment with corticosteroids. Open lung biopsy examination showed desquamative interstitial pneumonia. Only a single ferruginous body was seen on frozen section, but tissue examination by electron microscopy showed an extraordinary pulmonary burden of mineral dust with especially high concentrations of chrysotile asbestos fibres. This report emphasises the need to consider asbestos fibre as an agent in the aetiology of desquamative interstitial pneumonia. The coexistent slight interstitial fibrosis present in this case is also considered to have resulted from exposure to mineral dust, particularly ultramicroscopic asbestos fibres.

Desquamative interstitial pneumonia (DIP) was described by Liebow *et al*¹ as an idiopathic form of interstitial pneumonitis characterised by intra-alveolar collections of cells. These cells were originally believed to be desquamated alveolar epithelial cells but were subsequently recognised as large reactive alveolar macrophages.^{1,2} The name desquamative has nevertheless been retained to categorise this interstitial pneumonitis because this

pathological pattern was associated with a better prognosis, a more consistent response to steroid treatment, and longer survival.¹ No single specific aetiology has been determined for DIP.

The case presented here provides evidence that inhalation of mineral dust, including high concentrations of asbestos fibre, may produce the tissue reaction patterns of DIP as well as the more characteristic interstitial pulmonary fibrosis. This represents, to our knowledge, the first reported case of DIP in which the presence of asbestos fibre has been confirmed by tissue study. The analysis showed that although over 90% of the 820 million fibres/g of wet lung tissue were 3 μ m or less in length, sufficient numbers of fibres greater than 5 μ m in length were present, which could also account for the tissue response. These unusual findings prompted our detailed study and reporting of the apparent relations among asbestos fibre, DIP, and interstitial fibrosis.

Case report

The patient was employed in drywall construction for 32 years when he was exposed to components of

Figure 1 Pre-treatment posterior-anterior chest radiograph showing bilateral fine interstitial opacities.

Department of Pathology, Mount Sinai Hospital
J A Freed, R E Gordon, J Kleinerman
The Pulmonary Laboratory, Division of Pulmonary
Disease, Mount Sinai Hospital, New York
A Miller
Division of Environmental and Occupational
Medicine, Mount Sinai School of Medicine of the
City University of New York
A Fischbein
Environmental Sciences Laboratory, Institute of
Applied Sciences, Brooklyn College of the City
University of New York, NY 11210
A M Langer

Table 1 Results of pulmonary function tests

	7 August 1985	14 February 1986	22 January 1987
Vital capacity (l)	4.20 (88)*		4.41 (93)
FVC (l)	3.86 (81)	4.00 (84)	4.52 (96)
FEV ₁ (l)	2.66 (76)	2.76 (80)	2.83 (83)
FEV ₁ /FVC	0.69	0.69	0.63
Forced expiratory flow 25–75%, (l/sec)	1.91 (55)	1.67 (48)	1.45 (42)
Maximum voluntary ventilation (l/min)	103 (89)	120 (104)	124 (109)
Total lung capacity (l)	7.51 (102)		9.12 (124)
Residual volume (l)	3.31 (127)		4.71 (178)
Functional residual capacity (l)	4.31		5.36
D _L coSB (ml/min/mmHg)	137 (55)†	13.5 (55)	10.6 (44)
Single breath total lung capacity (l)	5.63	5.65	8.14

*Values in parentheses are percentages of predicted values

†Predicted values for D_LcoSB are adjusted for smoking habit (current smoker).

taping and jointing compounds. Both mineral components of these formulations, and exposure to asbestos during sanding and finishing, have been previously reported.³ The patient was first evaluated at Mount Sinai Hospital on 7 August 1985 (aged 52) because of dyspnoea of three months duration, wheezing, and productive morning cough; he was short of breath on climbing one flight of stairs or walking one block. He smoked three packs of cigarettes a day and had been an alcoholic until two years before evaluation. Previous illnesses included hypertension, acute myocardial infarction in 1978, duodenal ulcer, and microscopic haematuria and albuminuria first noted in 1983.

Physical examination was unremarkable except for raised blood pressure (150/100 mm Hg) and occasional ventricular premature beats. Chest radiographs showed fine interstitial opacities throughout both lungs, coded on the International Labour Office scale as S/P, 1/2 (fig 1), prominent hila, old rib fractures on the left, flattened hemidiaphragms, and increased retrosternal airspace on lateral view. The interstitial markings had progressed since 1983. There were no pleural abnormalities. A chest x ray film taken in connection with a clinical

field survey of drywall construction workers in 1973 showed no interstitial markings.

Results of routine laboratory tests included the following abnormalities: haemoglobin 17.7 g/dl, uric acid 8.2–10.5 mg/dl, cholesterol 375–466 mg/dl, albumin 2.8–3.0 g/dl, 25–30 red blood cells/high power field on urinalysis with 4+ albuminuria and 3.1 g protein/24 h. The blood urea nitrogen and creatinine concentrations, serum electrophoresis, antinuclear antibody, and latex fixation test were normal. Gallium scan showed a large area of slightly increased activity in the chest. A Kveim–Siltzbach test for sarcoidosis was negative.

Pulmonary function studies (table 1) showed normal lung volumes (vital capacity 88% of predicted) with slight airway obstruction (forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) 0.69). The single breath carbon monoxide diffusing capacity (D_LcoSB) was moderately reduced (55% of the smoking specific predicted value⁴ and the PaO₂ was normal at rest. The alveolar arterial O₂ difference (A–a Po₂) was 13 torr at rest and increased to 37 torr at maximum exercise, a value which is probably within normal limits. The excessive ventilation and dead space (0.48 at rest) were considered

Table 2 Results of incremental exercise testing

	15 October 1985	22 January 1987
Maximum ventilation (V _E ; l/min)	114 (104)*	110 (91)
Maximum oxygen consumption Vo ₂ (l/min)	2.12 (85)	2.36 (94)
(ml/kg/min)	27	32
Maximum heart rate (beats/min)	130 (77)	127 (75)
Maximum work rate (Kpm)	747	551
Watts	122	90
Dead space/tidal volume, rest	0.48	0.50
At Vo ₂ 1.0 l	0.39	0.43
Anaerobic threshold, (AT; l)	1.37	1.53
Delta V _E /Delta Vo ₂ (pre-AT)	40	37
Arterial Po ₂ (mmHg), rest	92	85
Max	80	76
A-a Po ₂ (mmHg), rest	13	8
Max	37	33

*Values in parentheses are percentages of predicted values

Figure 2 Bronchoscopic biopsy showing marked alveolar septal thickening with diffuse lymphocytic interstitial infiltrate and scattered lymphocytic follicles within septa (haematoxylin-eosin stain; original magnification $40\times$).

characteristic of diffuse pulmonary disease (table 2).

Bronchoalveolar lavage results were 45×10^6 cells, 82% alveolar macrophages, 11% eosinophils, 5% polymorphonuclear leucocytes, and 2% lymphocytes.

Bronchoscopic biopsy performed on 15 October 1985 showed obvious alveolar septal thickening with a diffuse lymphocytic interstitial infiltrate that also formed scattered lymphocytic follicles within septa (fig 2). Germinal centres were not present. There were clusters of macrophages in alveolar spaces. Trichrome stain showed early mild interstitial fibrosis. Neither asbestos bodies nor uncoated fibres were seen. Analytical electron microscopical examination of a carbon extracted biopsy specimen (about $1 \times 2 \times 0.005$ mm) by the protocol of Langer *et al*⁵ showed that it contained a variety of mineral dusts,

including both quartz and probably fibrous talc. None of the common asbestos fibres were detected. The report noted that the small size of the specimen placed limitations on any conclusions which might be drawn concerning inorganic agents in the aetiology of DIP.

Open lung biopsy performed on 3 December 1985 (left upper lobe) showed septal thickening and lymphocytic follicles, now with prominent germinal centres (fig 3). Alveolar pneumocytes were hyperplastic, and the intra-alveolar spaces were packed with large macrophages (fig 4) containing vesicular nuclei, some of which had an eosinophilic nuclear inclusion as noted by Pachefsky, *et al*⁶ in DIP. The macrophage cytoplasm was abundant and eosinophilic and contained granular haemosiderin. On electron microscopy, abundant chrysotile asbestos fibres of $3 \mu\text{m}$ in length were seen within the macrophage cytoplasm (fig 5). A single asbestos body was seen on frozen section (fig 6) but none were seen in paraffin sections. Trichrome stain showed mild interstitial fibrosis. The pathological changes were confluent in the subpleural region whereas the central lung tissue was normal in appearance.

Quantitative count of asbestos bodies by phase contrast microscopy on lung tissue digested by the method of Smith and Naylor⁷ gave 4666/g of wet tissue.

A specimen of bulk wet tissue (about 258 mg) was digested in 5% KOH, set in a hot water bath, and prepared for examination by analytical electron microscopy according to the technique outlined in Langer and Nolan.⁸ Mineral fibres were seen in the inorganic residues as follows: chrysotile asbestos, about 819×10^6 fibres/g of dry lung and tremolite, probably as cleavage fragments, about 20×10^6 /g of dry lung tissue were present. A talc fibre was found and particles of quartz, feldspar, micas, clays, and titanium dioxide were also detected.

Figure 3 Open lung biopsy of the left upper lobe showing macrophages filling alveolar spaces, septal thickening, and a lymphocytic follicle (haematoxylin-eosin stain; original magnification $40\times$).

Figure 4 Open lung biopsy of the left upper lobe showing hyperplastic alveolar pneumocytes and macrophages filling the alveolar space (haematoxylin-eosin stain; original magnification $200\times$).

Figure 5 Electron micrographs of interstitial and alveolar macrophages (A) exhibited many of the short fibres in lysosomes (B) (arrow), and free in the cytoplasm (C) (arrow). Micrograph (D) shows a typical small fibre from a digested tissue preparation from which the number of fibres and the size were calculated and electron microprobe analysis was performed to document that these were chrysotile fibres. Micrographs (A), (B), and (C) are of sections stained with uranyl acetate and lead citrate. A = 1920 $\times$, B = 52 000 $\times$, C = 66 000 $\times$, D = 40 000 $\times$.

Some 90% of the chrysotile fibres were shorter than 5 μm . Of the 60 grid openings scanned on the grid preparation, and the average number of fibres per grid opening (about 29), it may be extrapolated that asbestos bodies exist in a ratio of less than one in 1740 fibres in the pulmonary tissues. No asbestos bodies were encountered during this scan. The above fibre count is considered conservative in that clumps of chrysotile, consisting of 10s to 100s of individual fibrils, were counted as single fibres. The size of the chrysotile fibres/fibrils were such as to preclude visualisation by light optical microscopical techniques.

The patient was treated with prednisone (40 mg/day) with considerable clearing seen on his chest radiograph but no change in his respiratory symptoms or abnormal pulmonary function. The prednisone was tapered after four months and discontinued. The patient noted shortness of breath on bathing and dressing but did not discontinue smoking. The urine sediment showed trace blood, trace protein, 0–2 red blood cells/high power field and 0–2 white blood cells. The cholesterol concentration was lowered to 188 mg/dl by colestipol.

Discussion

Desquamative interstitial pneumonia in man has been reported in association with exposure to a variety of agents, including nitrofurantoin⁹ and cobalt in cemented tungsten carbide¹⁰ and complete Freund's adjuvant in rabbits.¹¹ Some cases, showing fibrosis, have had inconsistent immunological abnormalities.¹⁰ Focal forms have been described.¹² Some cases arise in association with intercurrent pulmonary disease.¹³ Most cases have been considered idiopathic.

Several reports mention an association between exposure to asbestos and DIP in man. In 1970, Corrin and Price reported a case of DIP in a dock worker in whom infrequent asbestos bodies were found. Asbestos fibres were not mentioned although tissue was examined by electron microscopy.² The patient had antinuclear antibodies in his serum, raising a doubt that his DIP was asbestos related. His disease remitted completely on treatment with corticosteroids. In 1971, Gaensler and Kaplan reported seven patients with asbestos pleural effusions, six of whom had biopsies taken.¹⁴ They found that, as well as the usual pattern of parenchymal fibrosis seen in

Figure 6 Open lung biopsy, frozen section, showing the sole asbestos body found in this case (haematoxylin-eosin stain; original magnification 400 $\times$).

each case, many sections showed haemosiderin laden macrophages along with "desquamated cells" densely packing alveolar spaces; in some sections they were more loosely packed. These were found in association with foreign body giant cells containing asbestos bodies. There were also areas showing a usual interstitial pneumonia (UIP)-like histology with hyaline membranes. Webster¹⁵ reported "desquamative alveolitis" in a miner with asbestos bodies, but the photograph and description suggest UIP, as there was significant interstitial fibrosis as well as partial organisation of alveolar spaces, which contained a few macrophages and (intra-alveolar) asbestos bodies. Thus it seems that only one case of classical DIP associated with exposure to asbestos has been reported in man.² Other cases show a mixed histological pattern of DIP and UIP and some show a predominantly UIP. These reported associations are weakened, however, by the omission of lung tissue analysis to determine mineral dust and asbestos fibre burden.

Animal experiments have occasionally supported an association between DIP and exposure to asbestos. Davis,¹⁶ before Liebow's initial description of DIP,¹ reported DIP-like histological findings in rats and guinea pigs inhaling chrysotile asbestos fibres. Although the usual reaction was a fibrosing UIP throughout the lung, in some animals—more frequently in guinea pigs than in rats—portions of lung tissue were completely consolidated, filled with macrophages, lymphocytes, and plasmacytes. In guinea pigs no resolution of the pneumonic process occurred for the five months after stopping inhalation of dust. This did not, however, progress to interstitial fibrosis. In this study, the asbestos fibres were clustered with most fibres being 3–4 μ m long. Lemaire *et al* administered short chrysotile asbestos fibres intratracheally to rats, producing an intra-alveolar accumulation of mononuclear cells in small clusters, obliterating alveolar lumina.¹⁷ Focal septal

thickening with a mononuclear cell infiltrate also occurred. Even after two months of exposure, the alveolitis persisted without producing fibrosis.

The fibrogenic potential of short chrysotile asbestos fibres is not entirely settled. In man, Nakamura¹⁸ reported that asbestos fibres of unspecified type and shorter than 1 μ m produced asbestosis in 21% of workers after 5–10 years of exposure and in 100% after 20 years. Bossard *et al* reported asbestosis in two of four workers exposed to short chrysotile fibres (90% less than 2 μ m in length).¹⁹

Exposure to short asbestos fibres in animals is reported to produce fibrosis inconsistently. Thus Vorwald *et al*,²⁰ Gross,²¹ Gardner,²² Klosterkotter,²³ and Burger and Engelbrecht²⁴ reported little or no fibrosis as a result of exposure to short fibres, whereas King *et al*,²⁵ Halt and colleagues,^{26–28} and Hiatt *et al*^{29–30} showed definite pulmonary fibrosis as a result of exposure to these fibres. These variable effects may be the result of different methods of preparing the asbestos fibres,²⁵ differences in delivery of the fibre dose to the lung, and species differences in the test animal.

In our case, however, there are sufficient quantities of fibre greater than 5 μ m in length to act as an agent in the aetiology of any of the asbestos diseases.

Another issue raised by our case is the risk of asbestos disease in drywall workers. The sanding process produces significant numbers of airborne chrysotile asbestos fibres.³¹ Fischbein *et al* found radiological evidence of asbestosis in 40.9% of drywall workers.³¹ Interstitial fibrosis was found on a lung biopsy in one drywall worker with lung carcinoma.³² As in our case, only ultramicroscopic asbestos fibres were seen. These included both long and short fibres, however.

In summary, the association of DIP with exposure to asbestos in man is not commonly reported. This may be due to the relative infrequency with which cases diagnosed clinically as asbestosis are subjected to biopsy. This case report is the first to document an association between DIP and a heavy occupational exposure to asbestos. Almost 820 million chrysotile fibres/g of dry lung tissue were found, high in the range of values anticipated for occupational exposure.⁸ Importantly, no fibres were visible on light microscopy. We conclude that asbestos should be considered as one of the agents in the aetiology of this case of DIP.

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Requests for reprints to: Dr A Miller, Pulmonary Laboratory, Box 1232, Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY 10029, USA.

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