

Polyvinyl chloride pneumoconiosis¹

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Arnaud, A., Pommier de Santi, P., Garbe, L., Payan, H., and Charpin, J. (1978). *Thorax*, 33, 19-25. Polyvinyl chloride pneumoconiosis. A 53-year-old man, who had been exposed for 23 years to polyvinyl chloride (PVC) in the bagging area of a vinyl chloride polymerisation plant, presented with a diffuse micronodular infiltrate on his chest radiograph. Light microscopy of lung obtained by drill biopsy showed a diffuse infiltration with histiocytes and multinucleated giant cells, with some collagen formation. Ultrastructural studies showed foreign particles in the macrophages, which were identical with PVC powder viewed under the electron microscope. Incubation of PVC powder with human lung macrophages *in vitro* showed that the macrophages engulfed the powder to give a similar ultrastructural appearance.

Pneumoconiosis due to polyvinyl chloride (PVC) was first described by Szende *et al.* (1970). Several epidemiological studies have since been made, which tend to demonstrate that PVC or vinyl chloride (VC) inhalation may be responsible for abnormalities of pulmonary function and chest radiograph (Lilis *et al.*, 1975, 1976; Miller *et al.*, 1975; Suciu *et al.*, 1975). However, histopathological descriptions of this disease are infrequent. We describe here one such case and a study of the ultrastructure of a lung biopsy specimen.

Case report

A 53-year-old man was referred in April 1974 for investigation of diffuse micronodular chest radiographic abnormalities (Fig. 1). He gave a history of chronic productive morning cough for three years, and for three months he had noticed mild weakness and slight exertional dyspnoea. He had smoked 20 cigarettes a day since age 22.

The patient had worked from November 1945 until December 1968 in the PVC bagging area of a vinyl chloride polymerisation factory. Since 1969 he had worked as a shepherd. A chest radiograph performed in 1968 as a routine factory check-up showed the same micronodular shadows. No further investigations were done. Previous chest radiographs were said to have been normal. Physical examination was negative. A scratch

tuberculin skin test was weakly positive. Sputum examination for *Mycobacterium tuberculosis* on three specimens was negative.

The red blood cell count was: $4.19 \times 10^{12}/l$; haemoglobin 13.2 g/dl; leucocyte count $6.6 \times 10^9/l$ with 40% lymphocytes and 60% neutrophils; platelets $294 \times 10^9/l$; erythrocyte sedimentation rate 6 and 20 mm/h; cholesterol 2.11 g/l; total bilirubin 6 mg/l; serum alkaline phosphatase 53 U/l; SGOT 25 U/l; SGPT 39 U/l. Pulmonary function tests showed forced vital capacity 3.82 l (expected value 5.29 l); forced expiratory volume in 1 second 2.82 l (expected value 3.89 l). Arterial blood gases: P_{aO_2} 84 mmHg; P_{aCO_2} 40 mmHg; pH 7.39. Carbon monoxide transfer factor 32.14 ml/min/mmHg (predicted value 31.75 ml/min/mmHg) (10.7 mmol/min/kPa; 10.6 mmol/min/kPa). No abnormality was seen on bronchoscopy. A lung biopsy using Steel's pneumatic trephine was performed.

LIGHT MICROSCOPY

The lung specimen was, for the most part, diffusely infiltrated by histiocytes, in which were seen a few alveolar ducts (Fig. 2). The cytoplasm of these histiocytes contained clear vacuoles. Giant multinucleated cells with vacuolated cytoplasm were also present (Fig. 3). PAS and alcian blue stains were negative. Polarised light revealed no intravascular birefringent particles. The cells were arranged in a collagen matrix, which was of thinly fibrillar aspect; a few smooth muscle fibres were also seen.

¹Supported in part by the Institut National de la Santé et de la Recherche Médicale



Fig. 1 Chest radiograph showing diffuse micronodular infiltrate.



Fig. 2 Lung biopsy showing diffuse infiltration with histiocytes. (Haematoxylin and eosin $\times 36$)

Fig. 3

ELECTRON MICROGRAPH
The specimen was fixed in a cacodylate solution containing osmium tetroxide, dehydrated in alcohol, and embedded in lead citrate. The section was cut on a microtome.

The cytoplasm of the cells had thin, expanded chromatin clumps in the nucleus. The major part of the material surrounding the cell membrane, whose thickness was either greater than 50 nm and 50 nm. Between the layers covered by the membrane were small spaces. The Golgi system was not visible.

Electron micrograph
The PVC particles were small, whose size was about 100 nm.



Fig. 3 Clumps of histiocytes and some giant cells showing a finely varuolated cytoplasm.

ELECTRON MICROSCOPY

The specimen was fixed with 3.4% glutaraldehyde in a cacodylate buffer; post-fixation was with 2% osmium-tetroxide. The specimen was then dehydrated in acetone and embedded in Araldite. The sections were cut by a Reichert ultramicrotome, then stained with uranyl acetate and lead citrate. Examination and photographs were obtained by Philips EM 300 electronic microscope.

The cytoplasmic membrane of the macrophages had thin expansions; the nuclei were small, and chromatin was either irregularly disposed in clumps in the cytoplasm or placed against the nuclear membrane. The cytoplasm was, for the major part, infiltrated by a non-homogenous material surrounded by an electron dense membrane, whose outlines were irregular. This material was either granular or of a fluffy appearance; the granules were 0.3 to 0.4 microns in size (Figs 4 and 5). Between the phagosomes, thin cytoplasmic layers covered the organelles; the mitochondria were small in size and had well conserved cristae. The Golgi system was normal.

Electron microscopy of PVC powder

The PVC powder¹ was composed of oval grains, whose size varied from 0.5–0.3 to 1–0.3 microns

¹AFCOVYL®; Pecliney, 04 Saint Auban, France

These grains were connected by PVC bridges or by the interposition of smaller granules of 0.1 micron diameter (Fig. 6).

Phagocytosis of PVC powder by alveolar macrophages

Human alveolar macrophages were obtained by bronchial lavage. About 2 to 3×10^6 macrophages were incubated with 0.2 ml of PVC powder for 90 minutes at 37.5°C in a mixture of 20% of compound 199² and 80% of fetal calf serum³. The macrophages were then treated and examined with the electron microscope according to the method previously described. The absorption of the PVC particles in the cytoplasm of these cells was rapidly accomplished. The particles appeared in the phagosomes as either oval corpuscles or clusters which were variable in size (Figs 7 and 8). At this stage, the particles showed no evidence of degradation. Thinly granular lysosomal material was deposited against them. The cytoplasm of the macrophages contained mitochondria, bundles of microfilaments, and multiple lysosomes.

Discussion

In this case of discrete pulmonary fibrosis associ-

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Fig. 4 Histiocyte with a small eccentric nucleus (N); the cytoplasm is mostly occupied by irregularly outlined phagosomes containing a fluffy granular substance. Collagen fibres (C). (EM $\times 13\ 900$)

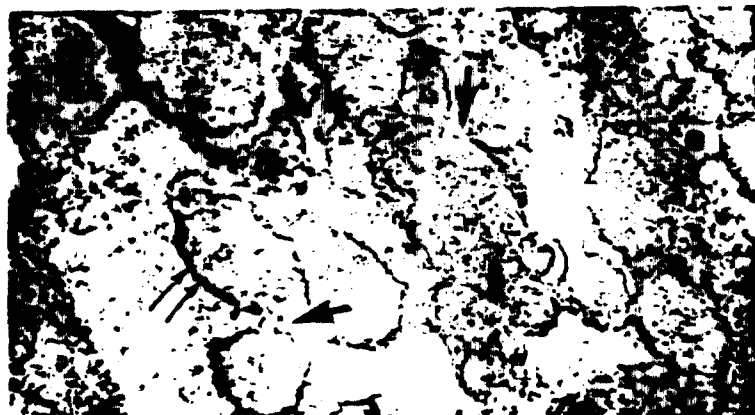


Fig. 5 Biopsy specimen; fluffy material with irregular outlines surrounded by a dense membrane (M). Phagosomes are confluent in places (C). (EM $\times 37\ 000$)

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Fig. 6 PVC powder made of oval subunits of variable size; they are linked together by smaller particles (—). (EM $\times 46\ 000$)

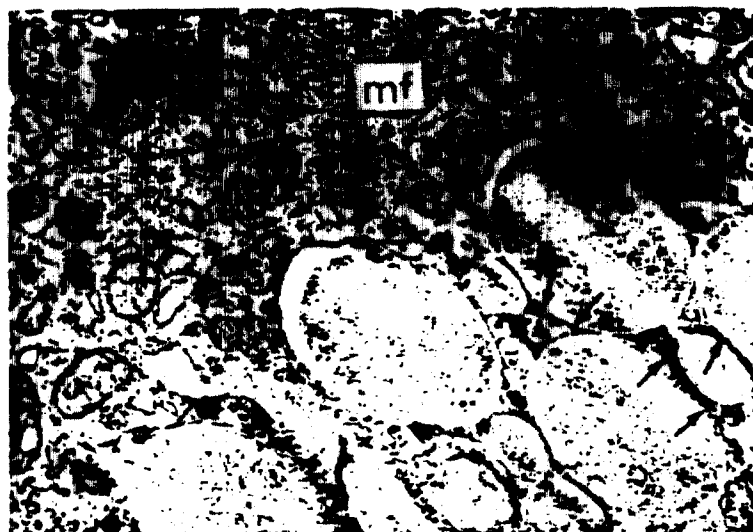


Fig. 7 In-vitro study of PVC particle phagocytosis by an alveolar macrophage showing oval bodies of uneven size with irregular outline, sometimes surrounded by finely granular lysosomal material (—); microfilaments (mf). (EM $\times 37\ 000$)

ated with a granulomatous reaction the lesions contained particles which could not be identified by the usual stains. We suggest that this may be pneumoconiosis induced by PVC inhalation.

The chest radiographic abnormalities in our patients are the same as those described by Liliš *et al.* (1975); these authors showed that 48.6% of workers exposed in their work to PVC dust for at least 20 years have reticular and/or micronodular chest radiographic shadows. The histological lesions we describe are identical with those recorded by Szende *et al.* (1970), who reported the case of a 31-year-old man who had worked for 12 months in an environment containing high

levels of PVC. This patient had severe respiratory failure. Pulmonary biopsy showed diffuse fibrosis associated with focal granulomatous lesions whose cells contained ovoid or polygonal particles. These lesions are the same as those experimentally provoked by Frongia *et al.* (1974), who exposed guinea-pigs and rats from two to seven months in a room where PVC powder was bagged. Examination of the guinea-pigs showed an earlier reaction at alveolar level composed of macrophages and giant multinucleated cells. These cells contained minute intracytoplasmic granules, which were not stained by the usual methods. On later examination, these lesions became focal granulo-



Fig. 8 In-vitro study of an alveolar macrophage in contact with PVC for 90 minutes. Particles of PVC are accumulated in a phagosome, which occupies almost all of the cytoplasm (—). Smaller phagosomes engulf oval corpuscles and small granules of PVC. (EM $\times 6800$)

mas. Examination of rats showed more pronounced initial fibrotic lesions but later lesions were comparable with those observed in the guinea-pigs.

The identical morphology of the intracellular foreign particles observed in our patient, and the microscopic appearances of the PVC powder and of the inclusions in human macrophages which have engulfed PVC powder *in vitro*, are convincing evidence that our case can be considered to be that of PVC pneumoconiosis.

Clinically, the evolution of PVC pneumoconiosis is uncertain. Our patient had only a slight reduction in vital capacity with no reduction in gas transfer factor, suggesting that the fibrosis was not as yet of much functional significance; on the other hand, Szende and co-workers (1970) reported a case with severe respiratory impairment. Occupational exposure to PVC dust may have been different in these two cases. Our patient was exposed to PVC dust only, while Lillis *et al.* (1975, 1976)

showed that PVC dust inhalation induced less severe respiratory function abnormalities than simultaneous inhalation of vinyl chloride monomer and PVC. This must be compared with the results described by Prodan *et al.* (1975), who showed that, in the guinea-pig, two hours' inhalation each day of air containing 10% vinyl chloride monomer over two weeks could produce diffuse pulmonary fibrosis. Further studies of the mechanisms of this pneumoconiosis are in progress.

We thank Dr. Allan Towne and Dr. Christiana Capo for their help.

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