Acute silicolipoproteinosis

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Xipell, J. M., Ham, K. N., Price, C. G., and Thomas, D. P. (1977). Thorax, 32, 104–111. Acute silicolipoproteinosis. A case of alveolar lipoproteinosis associated with silicosis is reported. A 58-year-old man had been exposed to silica for seven years and died three years after the onset of symptoms. Light microscopy of biopsy and necropsy material showed small silicotic nodules, silica particles, and alveolar lipoproteinosis, and ultrastructural studies were performed to define changes in alveolar epithelium and macrophages. The case provides a further example of alveolar lipoproteinosis developing as a response of the lung to injury by an external agent.

Lung disease due to exposure to silica has long been a well-known occupational hazard. Traditionally it is considered to be a chronic condition which develops after many years' exposure and results in slowly progressive pulmonary changes characterised morphologically by hyalinised collagenous nodules with late development of clinical symptoms.

Acute silicosis is a less frequently described entity associated with a relatively short exposure to silica dust, the rapid onset of symptoms, and a progressive downhill course not influenced by treatment. Recently, Buechner and Ansari (1969) drew attention to the occurrence of histological changes closely resembling alveolar proteinosis in a group of these patients. The case here reported draws further attention to the association of exposure to silica with the development of alveolar lipoproteinosis.

Case report

VB, a 58-year-old man, was referred in July 1974 for investigation of increasing bilateral pulmonary infiltration observed radiologically. The patient had complained of a persistent dry cough for two years and had noted shortness of breath on exertion for about seven months. He had been employed as a quartz miller for seven years and had previously worked as a dairy farmer for 20 years and in a brick works, pressing, cutting, and firing bricks for six years. Symptoms had developed shortly after the introduction of a piped forced clean air supply to the area of the machines used for quartz milling.

On physical examination, the blood pressure was 170/110 mmHg; no abnormal signs were elicited in the chest. A chest radiograph on admission showed enlargement of the hilar shadows and some retraction of the right upper lobe. Small nodular opacities about 3 mm in diameter were present in both upper zones and to a lesser extent in the midzones. The trachea was displaced to the right due in part to enlargement of the left lobe of the thyroid gland but also to the partially collapsed right upper lobe (Fig. 1).

Three years previously a chest radiograph had not revealed any abnormality in the lung fields, but one year before admission an abnormal linear pattern was first noticed.
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pattern had developed associated with a few small nodular opacities. These changes were thought to be due to silicosis and became more prominent over the next year.

The haemoglobin was 11·9 g/dl, serum iron 5·4 μmol/l (30 μg/100 ml), ESR 75 mm in 1 hour (Westergren), ANF positive (neutrophils and lymphocytes); examination for LE cells was repeatedly negative and the DNA binding assay was normal. The Mantoux test was negative up to 100 TU. Culture of sputum for acid-fast bacilli and fungi, and cytological examination for malignant cells were negative. The ventilatory function studies showed a restrictive defect with moderate impairment of gas exchange as shown by carbon monoxide transfer tests (See Table). No abnormality was noted on bronchoscopy. Erythrocytes and hyaline casts were found in the urine and renal function tests showed urinary protein 2·6 g/24 hours, urea 10·66 mmol/l (0·06 g/100 ml), and creatinine 0·15 mmol/l (0·017 g/l). A renal biopsy showed a focal glomerulonephritis.

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<tr>
<td>CO transfer</td>
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<tr>
<td>(mmol min⁻¹ kPa⁻¹)</td>
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<td>1974 1975 Predicted</td>
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<tr>
<td>3·685 2·345 4·690</td>
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<tr>
<td>(ml min⁻¹ mmHg⁻¹)</td>
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<td>11 7 14</td>
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COURSE

Readmission for further investigation of increasing breathlessness was precipitated early in 1975 by a deterioration in the patient's general condition associated with intellectual deterioration and recurring episodes of minor erratic behaviour.

The chest radiograph showed that the retracted right upper lobe was now quite opaque, and ill-defined coalescing fluffy shadows were noted throughout both lung fields. Elevation of the right hemidiaphragm had occurred during this time, indicating progressive loss of lung volume (Fig. 2).

Repeated investigation did not provide a definitive diagnosis of the pulmonary condition. Arterial blood gas studies were recorded as: pH 7·40, Po₂ 10·241 kPa (77 mmHg), PcO₂ 6·650 kPa (50 mmHg) at rest, with a marked arterial hypoxaemia on exercise (pH 7·45, Po₂ 6·916 kPa (52 mmHg), PCO₂ 4·921 kPa (37 mmHg)). The vital capacity had decreased from 2·65 l to 2·0 l (normal 3·78 l) with a forced expiratory volume in one second (FEV₁) of 1·80 l (normal 2·93). There was a moderately severe impairment of gas transfer with figures for CO uptake and CO transfer factor reduced to approximately half of predicted normal values, and considerably reduced compared with the figures one year previously (see Table).

The cause of the episodes of minor behavioural disturbance and the intellectual deterioration was considered to be transient attacks of cerebral ischaemia. Treatment with corticosteroids led to early neurological recovery, but attempted complete withdrawal of the steroids resulted in a recurrence of the symptoms, and prednisolone in low dosage was continued.

Lung and mediastinal node biopsies were performed 12 months after the original admission. The lung biopsy showed filling of alveolar spaces by eosinophilic acellular PAS positive material of finely granular form with cleft-like spaces scattered throughout (Figs 3 and 4). Alveolar walls were slightly thickened with an increase in reticulin fibres and a mild mononuclear cell infiltrate. Focal interstitial aggregates of lymphocytes were also present, particularly in relation to bronchi. There was a variable degree of pleural fibrous thickening and small acellular whorled fibrous nodules were present within the parenchyma (Fig. 3). Moderate numbers of birefringent particles were seen, particularly in relation to areas of fibrosis (Fig. 5).

Cultures of lung tissue for bacteria, including Mycobacterium tuberculosis, and for fungi were negative.

The lymph node showed replacement of normal architecture by nodular masses, consisting in part of hyalinised collagenous tissue but largely of non collagenous eosinophilic material which was

Fig. 2  Chest radiograph 12 months after original admission.
Fig. 3  Acellular material in alveoli and a fibrotic nodule. Haematoxylin and eosin ×40.

Fig. 4  Acellular PAS-positive material with cleft-like spaces in alveoli. Periodic acid-Schiff reaction ×100.
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patchily PAS positive. Scattered birefringent spicules were present throughout the node. The appearances were considered consistent with alveolar proteinosis and silicosis.

Whole lung bronchopulmonary lavage was carried out with some clinical improvement, but the patient died 15 months after presentation.

Necropsy

There was abundant tenacious mucoid material in the tracheobronchial tree. The right lung weighed 920 g, the left 940 g. Both lungs showed granular pallor, which in parts, particularly in the upper lobes, became confluent, and superimposed patchy congestion. Pulmonary arteries to segments of the right lower lobe contained adherent recent thrombi. Delicate fibrous adhesions were present in both pleural cavities. Hilar nodes were enlarged and contained nodular pale areas interspersed with deeply pigmented zones. The kidneys (right 174 g, left 180 g) showed moderate surface granularity. The stomach contained two chronic peptic ulcers on the lesser curvature. The thyroid (weight 60 g) was nodular with predominant enlargement of the left lobe.

Histology Sections of both lungs showed PAS collagenous nodules containing birefringent positive eosinophilic intra-alveolar material, small spicules, and subpleural and interstitial fibrosis similar to the biopsy sections. Areas of acute bronchopneumonia and a few clusters of cryptococci were also noted. Direct immunofluorescent examination showed focal intra-alveolar staining with antiserum against IgM and weaker similar staining with complement.

Sections of the kidneys showed focal glomerulonephritis. Direct immunofluorescence showed focal granular staining of peripheral capillary walls of some glomeruli with IgM, IgA, and complement. The appearances of the hilar lymph nodes were similar to that of the biopsy specimen. No abnormality was seen in brain sections.

Electron microscopy Tissue was fixed in 2% glutaraldehyde buffered with cacodylate, post fixed in 1% osmium tetroxide, and embedded in Spurr’s resin. Sections stained with uranyl nitrate and lead citrate were examined in a Siemens Elmiskop 1 at 60 kV. Alveolar walls were widened and contained a small amount of collagen. The occasional clusters of type 2 pneumocytes contained weakly osmiophilic lamellar bodies (Fig. 6). The alveoli contained cells which appeared to be of two types (Fig. 7). One type contained many small membrane bound lysosomes and phagocytic inclusion bodies but few myelin figures. The other cells,

Fig. 5  Birefringent particles in areas of fibrosis. Photographed in polarised light. H and E ×100.
Fig. 6  An intact type 2 pneumocyte shows the characteristic lamellar bodies and microvilli. EM ×6200.

Fig. 7  The two cell types found in alveolar spaces. The large cell contains lamellar bodies, fat droplets, and myelin figures. The smaller cell has many inclusions, few lamellar bodies, and resembles a macrophage. EM ×10 000.
usually larger in profile, contained many lamellar bodies, some weakly osmiophilic as in the type 2 pneumocytes, the remainder considerably more variable in size and conformation and intensely osmiophilic. Cell organelles were losing structural definition and there were many vacuoles, some fat droplets, and other degenerative inclusions. Some cells showed extensive degenerative change and could not be identified.

In regions in which cellular integrity had been completely lost, lamellar bodies lay free in alveolar spaces among organelle fragments and clumps of amorphous material. Occasional dense homogeneous, roughly polyhedral fragments of silica had torn from intra-alveolar cell cytoplasm and from debris during sectioning (Fig. 8).

Histologically the condition differs from typical silicosis in several aspects. The silicotic nodules are smaller and less frequent, as has been noted in the present case, or may be completely absent. The nodules are associated with interstitial fibrosis and pneumonitis, which changes are present diffusely throughout the lungs and are relatively prominent. Lymph nodes, although involved, show only small focal lesions and lack the typical fibrotic nodules which may be seen in the classical

Discussion

The clinical entity of acute silicosis had originally been described by Middleton in 1929. MacDonald et al. in 1930 observed albuminous material in alveoli in two cases of silicosis, and the Massachusetts General Hospital (1934) case records described postmortem findings of acute silicosis and pulmonary oedema. They noted pink staining intra-alveolar fluid which was considered to represent an extreme grade of oedema apparently with a very high protein content, and very few silicotic nodules. None of these workers, however, noted that this intra-alveolar material was PAS positive. No comparison of the material in human cases of acute silicosis with that of idiopathic alveolar proteinosis, as reported by Rosen et al. in 1958, had been made until the report by Buechner and Ansari (1969). The present case is similar to the four cases reported by these authors in that their patients presented with cough and progressive dyspnoea after an exposure to silica ranging from three to six years and averaging four years. The survival after the onset of symptoms is longer in this case than in any of those reported by them (77–455 days).
form of silicosis.

The alveolar spaces contain a proteinaceous material which is relatively cell free and strongly PAS positive, an appearance strikingly similar to that in idiopathic pulmonary alveolar proteinosis.

Ultrastructurally identifiable cells of two distinct morphological types are present among cellular and exudative debris in alveolar spaces. The preponderant cells resemble type 2 pneumocytes in their cytoplasmic components. Cells of similar morphology have been shown in the alveoli of iprindole-treated rats (Vijeyaratnam and Corrin, 1972; Fig. 4). Enzyme studies suggested that these cells were macrophages. However, the cellular effects of a systemically administered drug may not be strictly comparable with silica inhalation. Furthermore, the free alveolar cells are degenerate and surface specialisations have been lost. In their absence cytoplasmic components provide the only indication of cell type. The pattern of the endoplasmic reticulum and the lamellar bodies resembles that in the attached type 2 pneumocytes; lysosomes seen in clearly identifiable macrophages are lacking. No reports with illustrations of ultrastructural features in cases of silicosis associated with lipoproteinosis in man are available. There is, however, a report in abstract (Lamberty et al., 1973). This description is in accord with our findings.

A review of case studies of alveolar proteinosis shows that some authors consider that significant desquamation of type 2 pneumocytes occurs (Kuhn et al., 1966), or that marked proliferation of type 2 pneumocytes associated with some intra-alveolar pneumocytes is an early feature (Heppleston and Young, 1972). Others state that, at least in experimental situations, no sloughing of type 2 pneumocytes occurs, and the prominence of type 2 pneumocytes is a relatively late or minor change (Corrin and King, 1970; Vijeyaratnam and Corrin, 1973). These writers stress ingestion of extruded lamellar bodies by macrophages, the mobility of which is consequently seriously impaired. They suggest that these cells remain in the alveoli and eventually disintegrate, releasing their content and giving rise to the typical appearance of alveolar proteinosis.

Our observations support the views of Lamberty et al. (1973) and Kuhn et al. (1966). Despite the difficulties of interpretation of ultrastructure in postmortem material, we believe the alveolar cells to be largely pneumocytes, some still containing fragments of silica. This finding suggests that very small silica fragments, ingested by pneumocytes, would be initially inaccessible to macrophages and exert their toxic effects on epithelium. Macrophage activity in this material appears to be minimal, perhaps partly as a result of steroid therapy, but the possibility of interference with lipid metabolism cannot be completely discounted (Larson and Gordinier, 1965).

Davidson and Macleod (1969) examined the recorded cases of alveolar proteinosis and found that almost half had been exposed to various dusts or solvents, including silica, asbestos, cadmium, broken fluorescent tubes, chlorinated resins, titanium, and molybdenum. This suggested that alveolar proteinosis might be a response to a variety of inhaled irritants, a concept supported by the production of similar changes in experimental animals exposed to a variety of silica and non-silicaaceous dusts (Gross and deTreville, 1968; Corrin and King, 1970; Heppleston et al., 1970). Similar changes have been produced experimentally by ingested antidepressants (Vijeyaratnam and Corrin, 1973) and by the intraperitoneal introduction of chlorphentermine (Smith et al., 1973). Drugs, including busulphan (Littler et al., 1969), methotrexate, and chlorambucil (Spencer, personal communication) have also been associated with similar morphological pattern in the lung.

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