

Cyclophosphamide pneumonitis

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Cyclophosphamide pneumonitis. Cyclophosphamide can rarely cause interstitial pneumonitis and fibrosis. Although it has been reported previously in patients being treated for lymphoma, it occurred in this case in a man under treatment for glomerulonephritis. The temporal sequence of the respiratory insufficiency and the histopathology, when compared to the previous examples in the literature, suggest that cyclophosphamide was aetiologically responsible for the lung disease. There may be an interval of one or more months after discontinuation of cyclophosphamide therapy before clinical or radiological improvement occurs.

Cyclophosphamide is an alkylating agent which is utilised for its anti-neoplastic and anti-inflammatory properties. Inflammation or fibrosis induced by cyclophosphamide seems paradoxical. Nevertheless, a few reports indicate that cyclophosphamide may induce interstitial pulmonary inflammation and fibrosis. We report a patient in whom interstitial pneumonitis occurred during administration of cyclophosphamide and whose symptoms and radiographs improved when the drug was stopped.

Case report

A 25-year-old white man, who had previously been healthy, was admitted to hospital in March 1975 because of nephrotic syndrome. Renal biopsy showed membranoproliferative glomerulonephritis (dense deposit variety) with crescent formation and necrosis. Systemic blood pressure and renal function were normal and he was discharged on no treatment. During outpatient follow-up progressive systemic hypertension required treatment first with hydrochlorthiazide and later with methyldopa and hydralazine. The nephrotic syndrome persisted, and renal function, as measured by endogenous creatinine clearance, deteriorated from 125 ml/min in March to 20 ml/min in October, when he was readmitted to hospital. The patient was started on a combination of cyclophosphamide, 2.5 mg/kg/day, prednisone, 40 mg/day, dipyridamole, heparin, and frusemide.

He was readmitted on 17 December, 1975 because of the sudden onset of dry cough, dyspnoea,

fever, and chills. Physical findings were limited to a temperature of 102°F, tachypnoea, and crackles over the left posterior chest. A chest radiograph on admission showed patchy reticular densities in the left lower zone. The white cell count was 4.5×10^9 per l with a normal differential. Arterial blood gases on room air were pH 7.38, Po_2 37 mmHg, and PCO_2 24 mmHg. Repeated cultures of sputum and blood were negative. Cyclophosphamide and dipyridamole were discontinued on admission and prednisone was gradually reduced over one month. Fever persisted despite the administration of cephalothin and gentamicin for one week. Febrile agglutinins were negative. Acute and convalescent sera for viral and fungal antibody titres were not diagnostic. Antinuclear factor, cold haemagglutinins, and Coombs's test were negative. Serial chest radiographs showed an increasingly prominent reticular pattern, which gradually spread to involve all zones (Fig. 1). On 14 January, 1976, with the patient still febrile, dyspnoeic, and hypoxaemic, methyldopa and hydralazine were discontinued. Frusemide was now the only medication being given. Pulmonary function tests showed severe restriction and reduction in transfer factor. Oxygen was not administered. An open lung biopsy was performed on 23 January, 1976. Without any treatment the temperature gradually decreased and became normal on 9 February, 1976. Renal function deteriorated further and haemodialysis was begun.

During the year following lung biopsy the patient did well on haemodialysis and had no

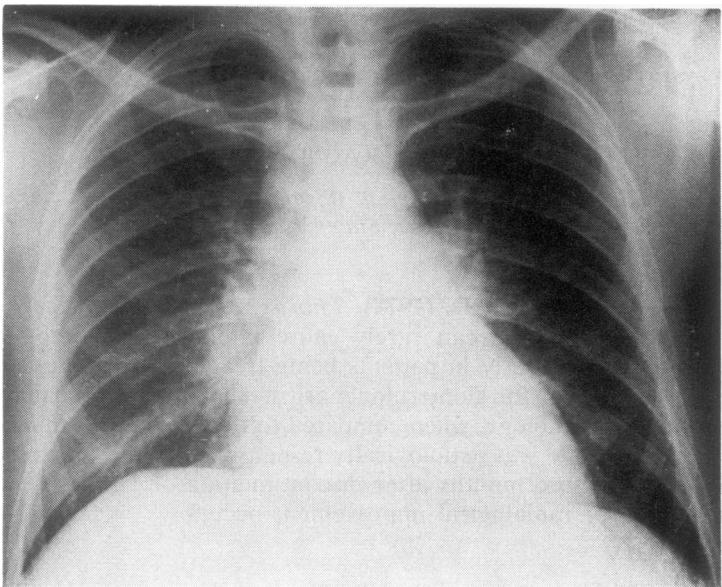


Fig. 1 Chest radiograph four days before lung biopsy. Reticular infiltrates are most prominent at the hila and extend to all lung fields.

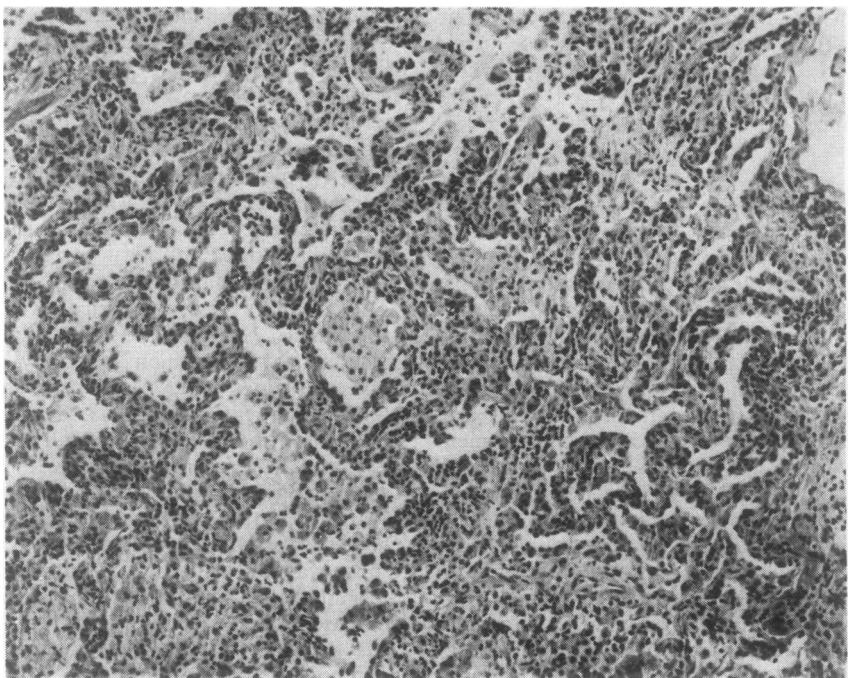


Fig. 2 Low magnification of lung biopsy. The architecture is obscured by an extensive intra-alveolar histiocytic infiltrate. Interalseptal septa are uniformly thickened (Haematoxylin and eosin $\times 125$).

respiratory symptoms. Chest radiographs showed gradual clearing. Repeat pulmonary function studies showed a marked improvement in the restrictive disease and a slight increase in transfer factor.

HISTOLOGICAL FINDINGS

The lung biopsy disclosed that approximately 50% of the alveoli and alveolar ducts were filled with desquamated granular pneumocytes and histiocytes (Fig. 2). These histiocytes had abundant vacuolated cytoplasm and contained a granular brown dust pigment that stained negatively by the periodic acid-Schiff reaction for glycoprotein and the Prussian blue reaction for iron. Among the intra-alveolar histiocytes were some polymorphonuclear leucocytes and red blood cells and a small amount of fibrin. Bronchiolar lumens, containing only a few cells, appeared prominent against the background of obscured alveoli (Fig. 3). The interalveolar septa were all thickened to 20–60 microns, due in part to an infiltrate of lymphocytes and plasma cells and in part to collagen, as demonstrated by the van Gieson connective tissue stain. Collagen was not

increased in the interlobular septa or around vessels. Granular pneumocytes were uniformly hyperplastic. They had enlarged, angular, hyperchromatic nuclei with moderate pleomorphism and an occasional prominent nucleolus. Cytoplasm was abundant and eosinophilic, giving these type II pneumocytes a cuboidal appearance (Fig. 4).

The pulmonary vessels, major bronchi, and pleura were normal.

Electron microscopy confirmed the hyperplasia of the type II pneumocytes, the interstitial inflammation, and the production of new interstitial collagen. Within the interstitium were occasional macrophages, which contained within their cytoplasm scroll-like inclusions, composed of parallel or convoluted tubular structures, which were bounded by a multilayered outer membrane. Cross sections of the tubular structures were similar to cross sections of cilia, but other definitive characteristics of cilia could not be identified. Endothelial cells were swollen. No viral inclusion was present.

The biopsy specimen of lung was cultured in various microbiological media. No aerobic or anaerobic bacteria, mycobacteria, fungi, or viruses could be isolated from it.

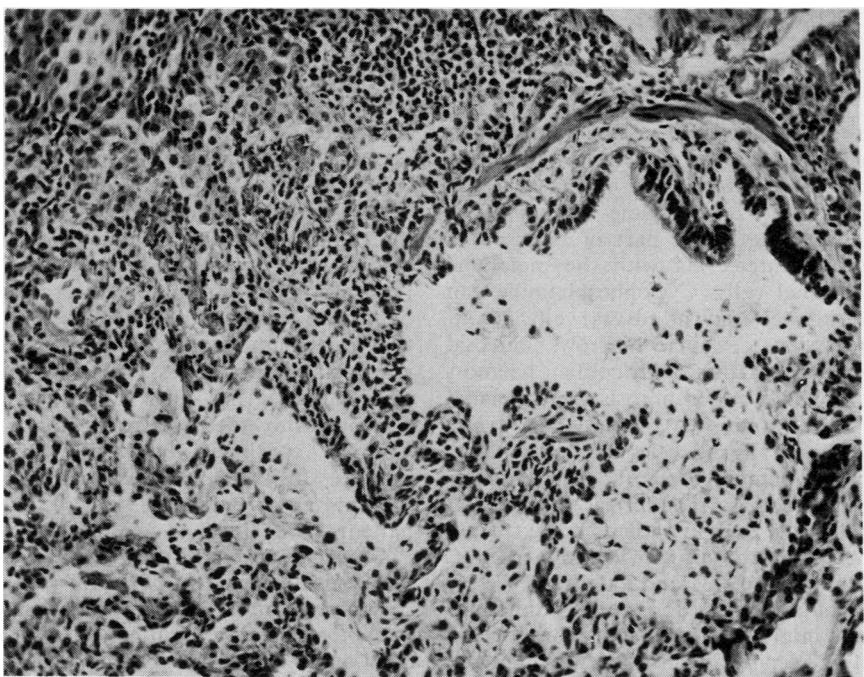


Fig. 3 Respiratory bronchiole with intact ciliated columnar epithelium (right). Lymphocytes aggregate adjacent to the smooth muscle of the bronchiole and diffusely infiltrate the interalveolar septa (*H and E* $\times 480$).

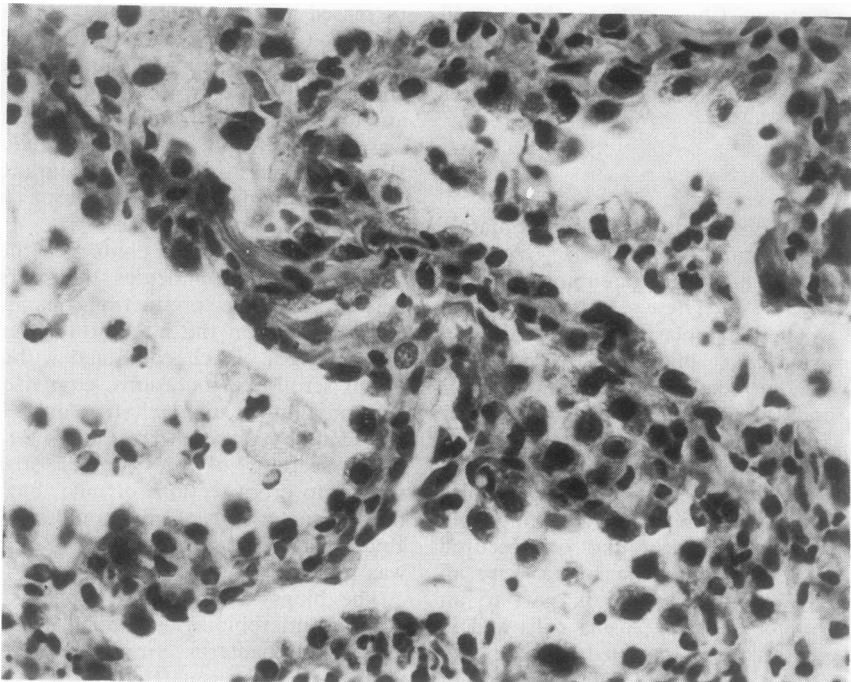


Fig. 4 High magnification of interalveolar septa. Alveolar lining cells have angular hyperchromatic nuclei and densely staining cytoplasm (*H and E* $\times 480$).

Discussion

Many drugs can elicit undesired pulmonary reactions (Rosenow, 1972). In some instances these reactions may be on the basis of hypersensitivity. In other instances, as with some antineoplastic agents, the drugs may exert part of their effect more directly by interfering with the metabolic function of normal cells. Cyclophosphamide can produce several well-known adverse effects, including suppression of bone marrow, mucosal ulceration with stomatitis and colitis, haemorrhagic cystitis with bladder fibrosis, and gonadal suppression. Pneumonitis attributable to cyclophosphamide therapy is much less common.

The five best documented records of pulmonary interstitial inflammation and fibrosis attributable to cyclophosphamide were in patients being treated for lymphoma. André *et al.* (1967), Dohner *et al.* (1972), Topilow *et al.* (1973), and Patel *et al.* (1976) all reported adults who developed pulmonary symptoms and interstitial infiltrates. Two of the patients died of respiratory insufficiency, and the other two patients recovered with disappearance of the infiltrates after discontinuation of cyclophosphamide. Rodin *et al.* (1970) reported a 3-

year-old child who developed lung infiltrates and died in respiratory distress. Duration of therapy with cyclophosphamide in these five patients was for a period between one and 36 months. This compares with two months of therapy in the present case. In these five earlier cases there was an interval of between one and seven months from cessation of therapy to the onset of sufficient respiratory distress either to prompt open lung biopsy or to cause death. This interval suggests that the inflammatory stimulus provided by cyclophosphamide continues for one or more months after the drug has been withdrawn. In the three patients who died in respiratory failure, this stimulus continued between three and seven months. In the other two patients and in the current report, the stimulus ceased and the patients recovered.

Other authors have mentioned an association of histologically proven interstitial pneumonitis with cyclophosphamide therapy but associated with *Pneumocystis carinii* infection, with therapy by additional chemotherapeutic agents known to produce pneumonitis, or with oxygen therapy (Karnofsky, 1967; Meschan *et al.*, 1969; Sohier and Nash, 1972; Stutz *et al.*, 1973). Retrospective inter-

pretation of the significance of the role of cyclophosphamide in these cases is difficult. Three examples of the association are alluded to in a review article but are not further described (Rosenow, 1972). Pulmonary oedema after intravenous administration of cyclophosphamide was also reported (Maxwell, 1974).

The histopathology of the cases previously reported is remarkably consistent. It includes moderate degrees of interstitial and subpleural lymphoid aggregates with only small numbers of neutrophils or eosinophils, hyperchromatic and pleomorphic granular pneumocytes, and fibroblastic proliferation, resulting in both septal widening and intra-alveolar fibrosis with segmental obliteration of pulmonary architecture. The histopathology described and depicted in these cases, including the abnormal nuclei of the granular pneumocytes, is seen again in the present case.

Because of the large number of known or suspected causes of interstitial pneumonitis, the linking of drug to pneumonitis in a causal relationship must be made with care. The histopathology is characteristic but not specific, and proof of the relationship must include the circumstantial evidence of drug therapy followed by pneumonitis and cessation of drug therapy followed by disappearance of pneumonitis, after other known causes of pneumonitis have been excluded. The present case fulfils this criterion in linking cyclophosphamide to interstitial pneumonitis and fibrosis.

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