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Pulmonary amyloidosis with impaired gas transfer

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This is the report of a patient with multiple myelomatosis in whom secondary amyloid infiltration of the lung produced impairment of gas transfer and death from respiratory failure.

Pulmonary deposits of amyloid may be found in the primary form of the disease (Gonzalez-Cueto *et al.*, 1970) or when it is secondary to other conditions (Dahlin, 1949). Respiratory insufficiency is uncommon (Prowse, 1958) but in a few patients may be fatal (Cotton and Jackson, 1964). This has been attributed to an 'alveolar-capillary block syndrome' (Spencer, 1968) but others have found no good evidence of a gas transfer defect (Bachmann, 1967 ; Mainwaring, Williams, Knight, and Bassett, 1969).

We now describe a patient with impaired gas transfer who died with pulmonary amyloidosis secondary to multiple myelomatosis.

CLINICAL PRESENTATION

In May 1968, a 58-year-old English lady presented with symptoms of increasing tiredness for two months and a loss of 7 kg in weight over the previous year. She was thin and mildly anaemic but showed no other physical signs of disease. She had smoked 20 cigarettes a day since the age of 13 years. Investigations showed that her haemoglobin was 10·6 g/100 ml, ESR (Westergren) 91 mm in one hour, and a paraprotein with a concentration of 0·6 g/100 ml was present in the α region of the serum electrophoretic pattern with a moderately low gamma globulin level. Immunoelectrophoresis showed the paraprotein to be of the Ig GL type. Her serum calcium was 9·1 mg/100 ml; inorganic phosphorus 3·5 mg/100 ml; alkaline phosphatase 6 King-Armstrong units/100 ml; serum albumin 4·6 g/100 ml; and blood urea 31 mg/100 ml. A trace of Bence-Jones protein was found in the urine. Plasma cells formed 25% of the total cell population of the bone marrow aspirate with many atypical forms. A skeletal survey showed no radiological changes.

A diagnosis of multiple myelomatosis was made and at that time the patient had no respiratory symptoms and the chest radiograph was normal.

TREATMENT AND PROGRESS

Treatment began in August 1968 with an intermittent high dosage of melphalan, 10 mg/day for 4 days, then 10 mg/day for 7 days. This latter course was repeated six times at intervals of 46 to 88 days, each further course being delayed until the white count and platelets had returned to normal. Prednisone, 20-60 mg/day for an average period of 20 days, was added after the fourth and subsequent courses because of bleeding due to severe thrombocytopaenia.

After 19 months the patient had gained weight, the paraprotein had completely disappeared, and the serum levels of immunoglobulins were normal. General weakness persisted although there was no clinical evidence of a neuropathy, myopathy or myasthenia. Sensory and motor conduction tests in the right ulnar and median nerves were normal. Persistent thrombocytopenia at this time prevented further melphalan being given.

In January 1970, 20 months after diagnosis, she developed breathlessness on exertion without orthopnoea or any clinical signs of respiratory or cardiac disease. The chest radiograph showed some fluid present in the right oblique fissure with linear atelectasis in the right middle lobe and an opacity at the left mid-zone (Fig. 1). No pathogens were cultured from the sputum. The haemoglobin at this time was 8·0 g/100 ml.

At 23 months, osteolytic lesions were found in many ribs with spontaneous fractures of the 6th, 7th, and 8th on the left side, and also in the skull, pelvis, and 6th thoracic vertebra. These were treated with continuous melphalan in low dosage,

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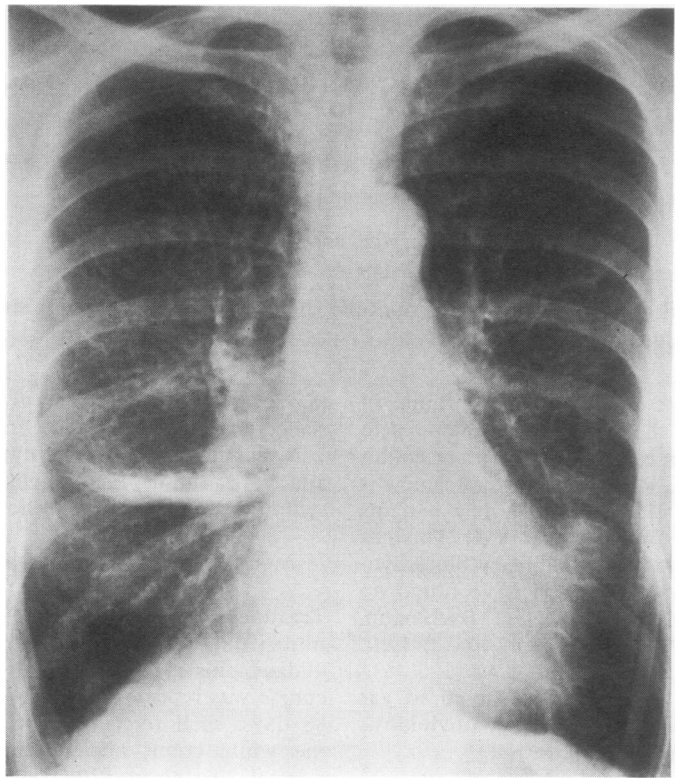

FIG. 1. *Postero-anterior chest radiograph taken approximately one month after the onset of breathlessness, 20 months after diagnosis of multiple myelomatosis, showing a lamellar shadow in the right lung and a rounded shadow in the left lung.*

0·25–0·5 mg/day and three doses of 500 rads of radiation to the rib fracture sites. This relieved her pain but the breathlessness steadily increased.

At 26 months, the haemoglobin had risen to 15·0 g/100 ml but the patient was unable to do even light housework because of breathlessness. She was referred to the Chest Unit for lung function investigations which were carried out with the patient sitting upright in a chair (see Table). The vital capacity and forced expiratory volume were recorded using a bell spirometer. Functional residual capacity and lung volumes were measured by the closed-circuit helium dilution technique (Gilson and Hugh-Jones, 1949) using a Warren Collins apparatus, and the gas transfer factor by the single breath method of Ogilvie, Forster, Blakemore, and Morton (1957). The arterial blood gases were analysed in a Radiometer electrode system with a correction factor for fluid/gas calibration difference for that particular instrument. These investigations showed the presence of a fixed

TABLE

PULMONARY FUNCTION TESTS[1]

Measurement	Result—Lt.		Predicted[2]	% Predicted
	Isoprenaline Before	After		
Vital capacity	1·9	1·9	2·2	86
Forced expired volume/sec	0·9	0·9	2·1	43
FEV_1/VC	48%		70–90%	
Total lung capacity	4·1		3·8	108
Residual volume	1·9		1·5	127
Functional residual capacity	2·6		1·7	153
RV/TLC	47%		39%	
Transfer factor	2·6		20·0	13
Kco	0·7		4·0	
Blood gas analysis			[3]	
Pa_{O_2}	71 mmHg		80–104	
Pa_{CO_2}	33 mmHg		35– 47	
pH	7·42		7·37–7·49	
Sa_{O_2}	95%[4]		90·5–101·0%	
Hco_3	21 mEq/l		23·8– 34·7	

[1] All volumes were corrected to BTPS
[2] Taken from Cotes (1968)
[3] From Comroe *et al.* (1962)
[4] Calculated by means of a Severinghaus slide rule (Severinghaus, 1966)

airflow obstruction since no improvement occurred following isoprenaline inhalation. There was no evidence of restrictive lung disease. The subdivisions of the lung volume, apart from functional residual capacity, were within the predicted range. The transfer factor showed a marked reduction compared with the expected value. The arterial oxygen saturation was normal at rest but the carbon dioxide tension was low, indicating alveolar hyperventilation. The normal pH indicates that, in the absence of any other cause for a reduced plasma bicarbonate, the hyperventilatory state was chronic and compensated.

After 29 months even more extensive bone disease was present. Irradiation again relieved local pain, 2,800 rads being given over the right humerus, 3,600 rads over the right chest, and 600 rads to the left clavicle. The breathlessness was now present even at rest and supplementary oxygen was given continuously at home. In December, 32 months after diagnosis, she was admitted because of dyspnoea so extreme that she could hardly speak. Crepitations were heard over both lungs but there was no sign of cardiac compensation. She continued to deteriorate despite general supportive treatment and died 48 hours after admission.

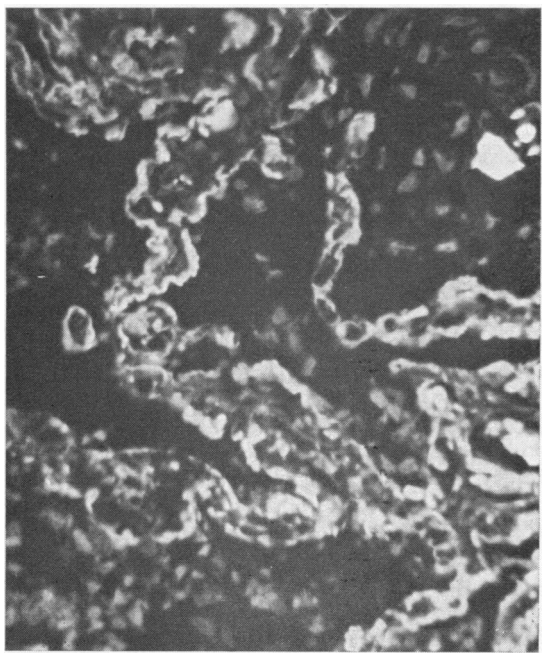

FIG. 2. *Pulmonary capillaries have a subendothelial layer of amyloid which fluoresces brightly. Alveoli contain histiocytes which are dimly fluorescent. (Thioflavin T, ultraviolet fluorescence* ×250).

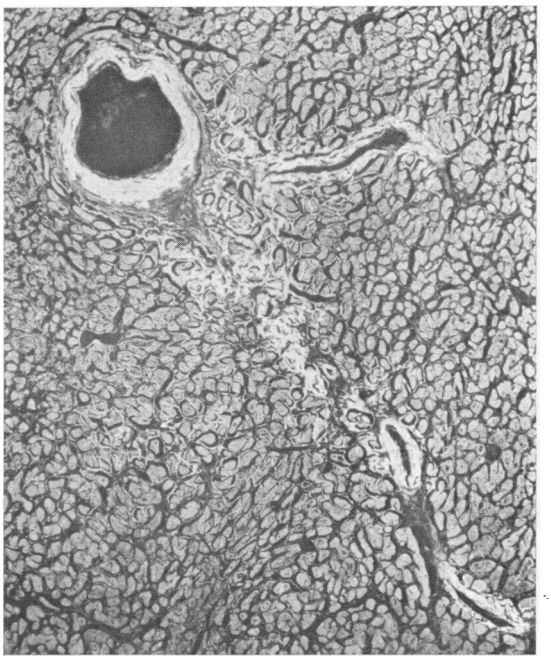

FIG. 3. *An artery in the myocardium with amyloid (bright fluorescence) replacing its muscle coat and extending between muscle fibres around the vessel and its branches. Close to the vessel the amyloid deposits are thick but further away there is a very thin layer around muscle fibres beneath the endothelium of capillaries and associated with the perimysial connective tissue. (Thioflavin T, ultraviolet fluorescence* ×80).

NECROPSY FINDINGS

In addition to myelomatous deposits in many bones, there was extensive amyloid deposition in the walls of veins, venules, arteries, and arterioles of all the tissues examined. The presence of amyloid was confirmed by staining with Congo red, thioflavin T, and crystal violet. It was also found related to capillaries, most prominently in the lungs (Fig. 2), myocardium (Fig. 3), and striated muscle (Fig. 4), but not in the capillaries of the liver, spleen, pancreas, adrenals, and pituitary, even though the involvement of arteries and arterioles in these organs was striking. The spleen, weighing 76 g, showed a marked reduction in the lymphocytic areas around the arterioles, the walls of the latter showing heavy amyloid infiltration. This reduction of lymphoid

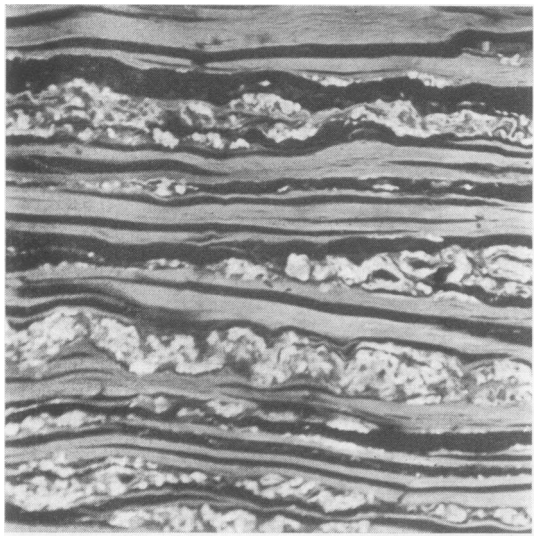

FIG. 4. *A longitudinal section from psoas major shows amyloid (bright fluorescence) in the walls of capillaries between muscle fibres. (Thioflavin T, ultraviolet fluorescence* ×250).

tissue may have been the result of melphalan and steroid therapy. The kidneys (left 140 g, right 132 g) showed no macroscopic abnormality, but amyloid was present in the media of some of the intralobular arteries and arterioles. None was seen in the capillary walls of the glomeruli although a little was present in the walls of the capillaries among the tubules.

The lungs appeared firm and brown, the right weighing 642 g and the left 550 g. No local cause could be found for the collapse of a small segment of the right middle lobe. There was heavy perivascular amyloid deposition, as described above, with complete replacement of the muscle coats of some arterioles and giant cells applied to the deposits (Fig. 5). None of the vessels was occluded. The alveolar capillaries had a thin layer of amyloid, up to 1 μ thick, external to the endothelium so that, especially in fluorescent preparations, the alveolar pattern was accentuated.

No signs of acute or continuing inflammation were present in the lungs and no excess of bronchial mucus-secreting cells. Some alveoli contained many haemosiderin-laden phagocytes but no unusual cells were seen which might correspond with the 'atypical epithelial cells' discussed by Heard and Cooke (1968). The alveoli were of average dimensions. There was a small quantity of carbon in the connective tissue around large vessels but no abnormal fibrous tissue was present.

DISCUSSION

The association of amyloidosis and myelomatosis has been recognized for many years (Stewart, 1938). Amyloid infiltration of the alveolar capillary membrane and vessels has been observed and pathologists inferred that the so-called alveolar capillary block syndrome should occur in this situation, but definite evidence of impaired gas transfer has been lacking, although Zundel and Prior (1971) reported a reduced carbon monoxide uptake in their patient with primary amyloidosis in the lung. The outstanding finding in the present case was a marked decrease in the gas transfer factor.

Finley, Swenson, and Comroe (1962) question the traditional concept of a diffusion barrier sufficiently great to produce arterial desaturation on exercise. They suggest that uneven distribution of ventilation in relation to perfusion and artery to vein shunting of blood are the true defects causing deficient gas transfer in the alveolar capillary block syndrome. The pathological findings in our case lend support to this view. There was no marked thickening of the alveolar septal walls, no fibrosis, and no significant cellular infiltration or loss of surface area, but there was extensive amyloid infiltration of arterial and capillary walls.

The tests of ventilatory function show no evidence of the restrictive lung lesion usually produced by fibrotic or extensive cellular infiltration of the parenchyma. The forced expired volume and FEV_1/VC ratio indicate a moderate degree of airflow obstruction. This could have been the result of chronic bronchitis since the patient was an urban dweller who had smoked 20 cigarettes a day for 47 years. However, at necropsy changes of chronic bronchitis were not found in the bronchial tree and there was no evidence of emphysema. Mainwaring *et al.* (1969) described wheezing and recurrent respiratory infection in their patient with amyloidosis of the lower respiratory tract. Prowse (1958), in his review of previously reported cases, states that wheezing and breathlessness were common symptoms. Indeed, repeated respiratory infection and haemoptysis were characteristic of the condition. Unfortunately, no ventilatory measurements were made in any of the 18 patients reviewed but 11 of them showed amyloid infiltration of the submucosal layers of the bronchi. We were unable to find such infiltration in our patient. Gonzalez-Cueto demonstrated fragmentation and loss of alveolar interstitial elastic fibres in the case he described (Gonzalez-Cueto *et al.*, 1970). It is possible that

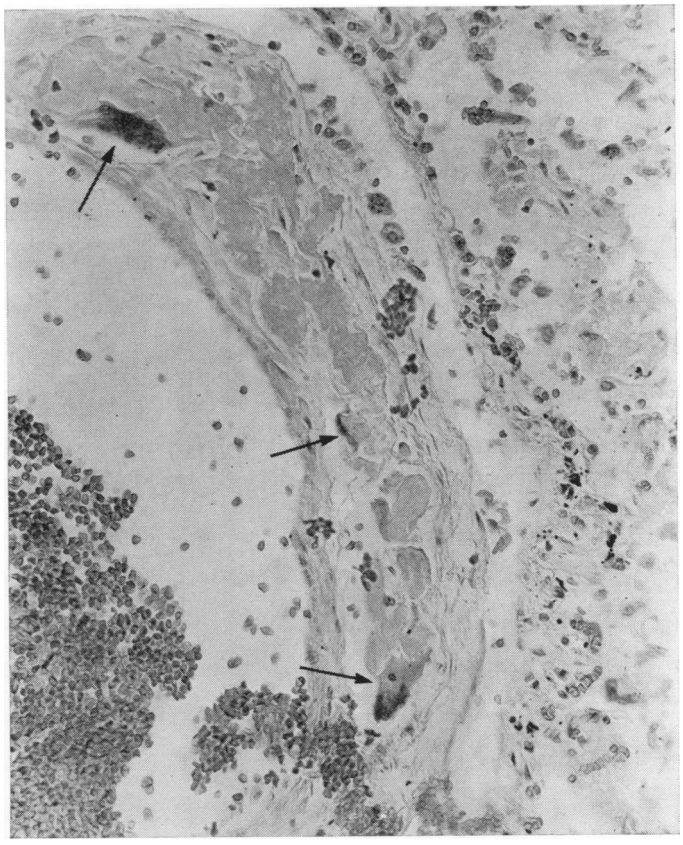

FIG. 5. *Multinucleate giant cells (arrowed) are associated with amyloid deposits occupying the muscle coat of a medium sized pulmonary vessel. Very little muscle remains. (Haematoxylin and eosin* ×320).

the amyloid infiltration altered the recoil tension characteristics of the lung parenchyma, allowing collapse of the small airways on forced expiration. We have no measurements of lung compliance but the increased functional residual capacity would be in keeping with this hypothesis. Thus the hyperinflation would help maintain patency of the collapsible airways during normal expiration, a circumstance similar to that seen in exacerbations of asthma.

The myelomatosis in the present case was treated with melphalan but it is unlikely that the pulmonary changes were caused by this drug. In particular, there was no sign of fibrinous exudate, intra-alveolar fibrosis, or atypical epithelial cells in the alveoli or bronchial epithelium changes as reported by Heard and Cooke (1968) after prolonged use of another alkylating agent, busulphan (Myleran). The histological picture also showed none of the features associated with radiation damage and the breathlessness predated the radiotherapy by several months.

The heart showed significant amyloid disease at necropsy but cardiac signs and symptoms were not a feature of the patient's last few months of life and cardiac failure would not in any case produce such a marked fall in the gas transfer factor with a well maintained vital capacity.

We therefore conclude that amyloidosis of the lungs was the main cause of breathlessness and that the reduction in gas transfer was due to amyloid infiltration of the alveolar vessels.

May we thank Dr. P. Hugh-Jones and the staff of his laboratory for the pulmonary function investigations; also Professor J. Anderson for allowing us to report the patient who was under his care. Professor W. M. Davidson and Dr. P. Flute of the Haematology Department gave us considerable help with the manuscript, and Professor E. A. Wright generously provided the necropsy facilities. May we also thank Miss M. Howell for typing the manuscript.

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