Fibrosing alveolitis with autoimmune haemolytic anaemia: two case reports

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Scadding, J. W. (1977). Thorax, 32, 134–139. Fibrosing alveolitis with autoimmune haemolytic anaemia: two case reports. Two patients with fibrosing alveolitis and autoimmune haemolytic anaemia are described. One patient also had neurofibromatosis. The haematological associations of fibrosing alveolitis are discussed, and a possible relationship between autoimmune haemolysis and fibrosing alveolitis is suggested.

In the last few years cryptogenic fibrosing alveolitis has been described in association with many different diseases (see reviews of Turner Warwick (1972) and Scadding (1974) but there has been special interest in systemic disorders involving abnormal immune mechanisms, particularly rheumatoid arthritis and systemic lupus erythematosus (Turner Warwick, 1974). Immunofluorescent studies on lung biopsies in patients with 'lone' fibrosing alveolitis, but with circulating antinuclear antibody in the sera, have shown deposits of gamma globulin and complement in alveolar walls (Turner Warwick and Haslam, 1971), and it has been postulated that immune complex deposition in alveolar walls may be the initiating factor in alveolar wall fibrosis in these patients (Turner Warwick, 1974). In autoimmune haemolytic anaemia, abnormal cell-bound circulating antibody is responsible for haemolysis. This pathological process has not previously been reported in association with fibrosing alveolitis. Two patients showing this association are reported here.

Case reports

CASE 1
A 62-year-old man was first admitted to hospital in November 1973 for stripping of varicose veins. Investigations included a haemoglobin of 14·4 g/dl and a chest radiograph, reported as showing minimal mottling at both bases. Ten days postoperatively he developed right-sided pleuritic pain, fever, and a dry cough. This resolved with antibiotic treatment. In February 1974, a follow-up radio-

graph showed persisting basal shadowing (Fig. 1) at a time when the patient was asymptomatic. In July 1974 he had recurrent right-sided pleurisy with fever, cough, and purulent sputum, again successfully treated with antibiotics. In November 1974, over a three-week period he developed severe symptoms of malaise, exertional dyspnoea, and exertional calf pain. He had lost 2 stones (12·7 kg) in weight over the previous year. He smoked 15 cigarettes daily. A family history revealed that his brother and maternal aunt both had pernicious anaemia.

He was referred to Brompton Hospital in December 1974 when, on examination, he was very pale and slightly jaundiced, and there was finger clubbing. There were several small pedunculated fleshy skin lesions on the trunk. Tongue and buccal mucosa were normal, and there was no lymphadenopathy nor arthritis. In the chest there were bilateral basal fine inspiratory crackles. There was mild bilateral ankle oedema and an apical mid-systolic cardiac murmur. A firm liver edge was palpable 4 cm below the right costal margin but the spleen was not palpable.

A chest radiograph taken in December 1974 is shown (Fig. 2). Lung function at this time is given in the second column of the Table, showing reduced volumes and a marked decrease in gas transfer. Arterial gases on air at rest were Po_2 11·1 kPa (83 mmHg) and Pco_2 5·1 kPa (38 mmHg). Histology of a lung biopsy showed the changes of fibrosing alveolitis, predominantly mural but with quite marked desquamation in places (Fig. 3).

Haemoglobin was 5·1 g/dl, white blood count 7·8×10^9 1^-1 (7800/µl), with a normal differential;
Fibrosing alveolitis with autoimmune haemolytic anaemia: two case reports

platelets $203 \times 10^9$ l$^{-1}$ (203 000/μl), ESR 40 mm/hour. A blood film revealed 32% reticulocytes with 8 normoblasts per 100 leucocytes. Sternal marrow aspirate showed very active erythropoiesis, partly megaloblastic, with depressed granulopoiesis. The direct Coombs' test was positive due to IgG on the red cell surface. On elution this IgG had marked Rhesus specificity with some anti-'e' specificity (Rhesus phenotype cde/cde). The serum contained autoantibody reacting against enzyme-treated red cells. Red cell survival studies (chromium-51) showed a red cell half-life of only 4 days

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Fig. 1 Case 1. Chest radiograph in February 1974 showing bilateral lower zone shadowing.

Fig. 2 Case 1. Chest radiograph in December 1974 showing persistent bilateral basal shadowing.
A painful, pedunculated skin lesion was excised from the patient's trunk, histology of which showed a neurofibroma with concentric fibrous strands enclosing small spindle-shaped cells.

Treatment initially with folic acid and B12 injections raised the haemoglobin to 8 g/dl, but no higher, and with no significant reduction in reticulocyte count. Subsequently, 60 mg of prednisone daily restored the haemoglobin to 15 g/dl over three weeks, with gradual reduction of reticulocytes to 0–2%. The direct Coombs' test became negative, though on one occasion since it has been weakly positive. A repeat chest radiograph 14 days after starting prednisone showed considerable clearing of the basal shadowing (Fig. 4), and lung function showed a striking increase in lung volumes and gas transfer (column 3, Table). The patient remains well on a small daily dose of prednisone and free of symptoms 10 months after starting treatment. Subsequent lung function tests have shown that the initial improvement has been maintained. The haemoglobin remains normal at 14–16 g/dl.

CASE 2
A 76-year-old man was found to have right apical

Fig. 3 Case 1. Lung biopsy in January 1975. Fibrosing alveolitis, showing mural thickening and an area of desquamative change. Haematoxylin and eosin ×170.
Fibrosing alveolitis with autoimmune haemolytic anaemia: two case reports

Fig. 4 Case 1. Chest radiograph 14 days after the beginning of prednisone treatment, showing clearing of lower zone shadowing.

lung shadowing at mass radiography in 1959 which was thought to be an inactive tuberculous lesion. Follow-up films showed no change, and no treatment was given. In 1967 he was investigated for symptoms of breathlessness, cough with sputum, and malaise. A chest radiograph again showed right apical shadowing. Tests for tuberculosis were negative, including a sputum smear and culture and a negative Heaf test. He was found to be anaemic with a haemoglobin of 60% and 6% reticulocytes and a strongly positive direct Coombs' test. A diagnosis of autoimmune haemolytic anaemia was made and he was treated with 30 mg of prednisone daily, with para-aminosalicylic acid and isoniazid cover. There was no reduction in haemolysis after two months, and all the drugs were stopped.

The patient complained of increasing dyspnoea, and chest radiographs over the next few months showed a gradually extending reticular shadowing in both lungs. Sputum was again negative for acid-fast bacilli and malignant cells. The patient was referred to Hammersmith Hospital in June 1968. On examination he was pale, but not dyspnoic or cyanosed, and there was no finger clubbing. Crackles were present throughout both lungs, particularly basal. A chest radiograph (Fig. 5) showed diffuse widespread reticular shadowing with some coarse basal honeycombing and persistent right apical shadowing. Tomography of the right apex showed thickened interstitial septa but no cavity formation. Lung function showed a vital capacity of 2.3 litres, forced expiratory volume in one second 2.15 l, total lung capacity 4.0 l, transfer factor (DLCO) 7.26 ml/min/mmHg (2.4 mmol min⁻¹ kPa⁻¹) (predicted 23; 7.7), and transfer factor per litre of lung volume (Kco) 2.28 min⁻¹ torr⁻¹ (17.1 min⁻¹ kPa⁻¹). Peak expiratory flow rate was 460 l/min. Bronchoscopy and bronchial biopsy were normal. In view of his age lung biopsy was not performed. The diagnosis made was fibrosing alveolitis. Haematological investigations revealed a haemoglobin of 10.9 g/dl with 7.2% reticulocytes, normal white count and differential; ESR 104 mm/1 hour. Direct Coombs' test was strongly positive. Antibody eluted from the red cells gave a strongly positive indirect Coombs' test and showed anti-E specificity (Rhesus phenotype cde/cde). Serum IgG was 24.00 g l⁻¹ (2400 mg/100 ml) and serum bilirubin 19 μmol l⁻¹ (1.1 mg/100 ml). Antinuclear antibody and LE cells were not detected. The results were typical of autoallergic haemolytic anaemia. Following these investigations the patient became lost to follow-up and no further clinical details are available.

Discussion

Few haematological abnormalities have been described in association with fibrosing alveolitis. In
a series of 154 patients with fibrosing alveolitis, Turner Warwick (1972) recorded one patient with myelosclerosis, two with purpura, two with pernicious anaemia, and one with folic acid deficiency. Gumpel (1971) described a patient with fibrosing alveolitis, Sjögren's syndrome, Waldenström's hypergammaglobulinaemia, and immune paresis. The association of autoimmune haemolytic anaemia with fibrosing alveolitis has not been described before, and this observation is of interest in view of the recent speculation that fibrosing alveolitis may, in some cases at least, be initiated by immune complex deposition in alveolar walls. However, circulating immune complexes are not formed in autoimmune haemolysis: the abnormal autoantibody, usually IgG, attaches to red cells, fixing complement to a variable degree. The coated red cells then become attached to splenic macrophages, which have specific receptor sites for IgG (LoBuglio et al., 1967). After attachment the red cells are either lysed, or part of the membrane is removed, with the formation of spheroid cells that are more susceptible to subsequent splenic destruction. A similar process of macrophage attachment is known to occur in the circulation, liver, and bone marrow (Dacie and Worlledge, 1975).

It is probable that pulmonary macrophages are also involved in this process since it has been shown that these cells originate in the bone marrow and may therefore be expected to share their functional characteristics. For example, Pinkett et al. (1966), using chromosome-labelled mouse macrophages, found that between 60% and 80% of free alveolar macrophages were derived from labelled bone marrow mononuclear cells. Bowden et al. (1969) and Velo and Spector (1973), using tritiated-thymidine-labelled macrophages, confirmed the bone marrow origin of free alveolar macrophages and found that before migration into alveolar spaces these cells spent two to three days within alveolar walls, presumably undergoing a process of further maturation. It is considered that a normal function of pulmonary macrophages is the removal of old red cells from the circulation (Spencer, 1968), and it seems likely that this activity is intensified in autoimmune haemolysis. It is suggested that an active phagocytosis by circulating macrophages and by macrophages in alveolar walls, with ingestion or red cell fragments containing immune complexes, may give rise to an inflammatory reaction within alveolar walls, leading eventually to fibrosis. In the first patient described here, red cell survival studies showed no excess destruction of cells by the spleen (shown to be present radiologically), with large excess counts over the liver, an unusual situation in autoimmune haemolytic anaemia. It may be that, in the absence of red cell destruction in the spleen, haemolysis occurs to a greater degree in extra-

Fig. 5 Case 2. Chest radiograph in June 1968. Widespread diffuse shadowing with lower zone honeycombing.
splenic sites, including liver and lungs. However, staining for haemosiderin in the lung biopsy from patient 1 did not show excessive deposits which might be expected in active haemolysis within the lungs.

It is possible that the fibrosing alveolitis in the two patients here occurred coincidentally with the autoimmune haemolytic anaemia, but the diseases are both uncommon and this raises the question of a pathological relationship. An alternative explanation in the first patient is that the fibrosing alveolitis was associated with the neurofibromatosis, now a well-recognised association (Massaro and Katz, 1966). In the first patient the dramatic response of the pulmonary abnormalities, as measured by lung function tests and radiographic appearances, and the rapid improvement in the anaemia, occurred concurrently with prednisone, but this itself cannot be taken as evidence of a pathological relationship between the two conditions. Corrections of the anaemia would lead to an improvement in lung function in the lungs (Cotes, 1965), but the improvement measured here is greater than would be due to such a correction alone, and the increase in lung volume and radiographic appearance both suggest an improvement in the fibrosing alveolitis itself.

The folate deficiency in this patient, and the initial response of his anaemia to folate therapy, are in keeping with the view of Chanarin et al. (1959) that folate deficiency is common in severe haemolytic states, leading to megaloblastic erythropoiesis as a result of an increased requirement of folic acid.

I am grateful to Dr. J. C. Batten and Professor C. M. Fletcher for permission to report details of patients under their care, to Dr. Shelia Worledge for performing the immunological studies in the first patient, to Dr. B. Heard for helpful comments on the histology, and to Mr. K. Moreman for the photomicrographs.

References


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Thorax 1977 32: 134-139
doi: 10.1136/thx.32.2.134

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