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Idiopathic pulmonary haemosiderosis: a form of microscopic polyarteritis?

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Abstract

Idiopathic pulmonary haemosiderosis remains a diagnosis of exclusion in patients who present with pulmonary alveolar haemorrhage. Systemic vasculitis developed in a patient with an eight year history of idiopathic pulmonary haemosiderosis. The diagnosis was confirmed by a rising titre of antineutrophil cytoplasmic antibodies directed against myeloperoxidase. Treatment with immunosuppressive agents resulted in complete resolution of symptoms and suppression of the antibodies. Measurement of antineutrophil cytoplasmic antibodies is recommended for all patients with pulmonar alveolar haemorrhage syndromes.

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Alveolar haemorrhage is a recognised mode of presentation of several diseases, including microscopic polyarteritis.[1 2] In many cases no underlying cause is found despite investigation. These cases are labelled as idiopathic pulmonary haemosiderosis,[2] which remains a diagnosis of exclusion. We report a case of idiopathic pulmonary haemosiderosis in which systemic vasculitis developed eight years after the original presentation with haemoptysis, anaemia, and shadowing on the chest radiograph. This case emphasises the value of the measurement of antineutrophil cytoplasmic antibodies in patients with pulmonary haemorrhage, particularly during an acute episode.[2]

Case report

A 22 year old man had presented eight years previously with recurrent haemoptysis. Investigations revealed iron deficiency anaemia and his chest radiograph showed diffuse alveolar shadowing. The bronchoscopic appearances were normal but bronchial washings showed hemosiderin laden macrophages. An associated but asymptomatic feature was jejunal villous atrophy consistent with adult coeliac disease. No underlying cause for the haemoptysis could be found (an autoantibody screen and test for antiglomerular basement antibodies gave negative results) and a diagnosis of idiopathic pulmonary haemosiderosis was made by exclusion. He was reviewed regularly and continued to have repeated episodes of minor, self limiting haemoptysis, usually after a chest infection. At no time were there any symptoms or signs of systemic disease. After eight years he developed increasing breathlessness on exertion and presented with severe haemoptysis precipitated by infection. Examination disclosed line crackles in the chest but no other abnormality. His blood pressure was 100/70 mm Hg. The chest radiograph showed diffuse alveolar shadowing. Other investigations showed: haemoglobin 10 g/dl with an iron deficient picture; erythrocyte sedimentation rate 80 mm in one hour; raised C reactive protein, 80 mg/l; raised plasma creatinine, 130 μmol/l; complement C3 and C4 levels and results of liver function tests normal; ^{51}Cr EDTA glomerular filtration rate 70 ml/min/1·73 m^2; proteinuria, 0·5 g/day; microscopic haematuria with red cell casts. Lung function tests performed five days after admission showed a restrictive ventilatory defect with reduced transfer factor for carbon monoxide corrected for alveolar volume (KCO); arterial blood gas analysis at presentation showed: oxygen tension 4·8 kPa, carbon dioxide, pH 7·48, bicarbonate tension 4·6 kPa, 27 (FIO_2 0·21) (table). The KCO remained low during the acute episode, possibly because the test was performed late as the KCO usually returns to normal within 48 hours.[2] In addition, the low KCO may reflect the underlying pulmonary fibrosis, which had developed as a result of repeated episodes of pulmonary haemorrhage. Anti-glomerular basement membrane antibodies were not found. Antineutrophil cytoplasmic antibody was present with cytoplasmic pattern (titre 1/80). Enzyme linked immunosorbent assay (ELISA) showed that these antibodies were directed against myeloperoxidase (titre 1/80) and not against serine proteinase 3. Serial studies on stored and subsequent serum samples are summarised in the figure. Renal biopsy showed segmental necrotising glomerulonephritis with crescents,

Results of serial pulmonary function tests

	*Predicted**	*1981*	*1987 (2 y before treatment)*	*Sept 1989 (3 mo before treatment)*	*Dec 1989 (acute illness)*	*June 1990 (follow up)*
FEV_1 (ml)	3660–4960	3630	2950	2570	2330	2580
FVC (ml)	4290–5810	4440	3760	3570	3290	3770
TLC (ml)	5330–7750	5350	5010	5060	4970	5000
TLCO (mmol/min/kPa)	9·98–13·5	8·92	4·71	4·11	3·32	4·37
KCO (mmol/min/kPa/l)	1·63–2·20	1·81	1·14	0·96	0·85	1·00

FEV_1—forced expiratory volume in one second; FVC—forced vital capacity; TLC—total lung capacity; TLCO—carbon monoxide transfer factor; KCO—transfer coefficient.

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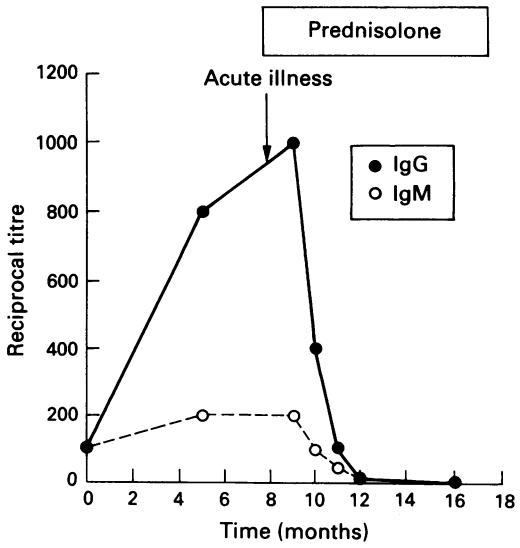

Titres of antineutrophil cytoplasmic antibodies as measured by indirect immunofluorescence from the time of the first sample (time 0), showing rising IgG titres until the acute illness. Titres fell rapidly after the introduction of immunosuppressive treatment.

and the negative immunoperoxidase staining of biopsy material was consistent with a diagnosis of microscopic polyarteritis. Treatment was started with intravenous pulse methylprednisolone 0·5 g three times a day, followed by oral corticosteroids 20 mg/day for four weeks tapering to a maintenance dose of 12·5 g/day over eight weeks, and cyclophosphamide 2·0 mg/kg/day. Azathioprine 1·5 mg/kg/day was substituted for cyclophosphamide after one month. After one year's follow up there has been no recurrence of symptoms and the patient is symptom free with maintenance immunosuppression (prednisolone 12·5 mg and azathioprine 125 mg/day. The titre of antineutrophil cytoplasmic antibodies has fallen to zero according to both ELISA and indirect immunofluorescence. Results of lung function studies remain abnormal but have improved since the acute illness. His glomerular filtration rate is now normal at 120 ml/min/1·73^2.

Discussion

Alveolar haemorrhage may occur in association with several diseases; the term idiopathic pulmonary haemosiderosis is used when all known causes of pulmonary alveolar haemorrhage have been excluded.[1] Our patient had long-standing pulmonary haemorrhage before the development of systemic symptoms. There was no evidence of systemic vasculitis during this period. His antineutrophil cytoplasmic antibodies titre became positive nine months before the start of his systemic illness and returned to normal with treatment, confirming his clinical and immunological remission. The coincidence of a rising antineutrophil cytoplasmic antibodies titre with acute alveolar haemorrhage supports the hypothesis that he had been suffering from a subclinical capillaritis which became overt both clinically and immunologically during his recent exacerbation.

Although the cause of idiopathic pulmonary haemosiderosis is unknown, an association with adult coeliac disease has been described, which suggests immune mechanisms.[1] Immunofluorescence[1] and electron microscopic[3] studies, however, have not shown features suggesting immunoglobulin or immune complex deposition, although ultrastructurally endothelial cell and capillary basement membrane damage has been observed.[3] Exacerbations of idiopathic pulmonary haemosiderosis may occur with symptoms of infection, as in this case, and we may speculate that, against the background of predisposing capillaritis, local inflammatory cell traffic, triggered by infection, results in an amplification of the capillaritis, further endothelial cell damage, and haemorrhage.

Antineutrophil cytoplasmic antibodies were directed against antigens found in the neutrophil primary granule.[4,6] Indirect immunofluorescence of ethanol fixed neutrophils shows two major categories of antineutrophil cytoplasmic antibodies—C-ANCA (cytoplasmic staining) and P-ANCA (perinuclear staining). Most C-ANCA antibodies are directed against the antigen serine protease III, whereas most P-ANCA are directed against the antigen myeloperoxidase. Autoantibodies to either serine protease III or myeloperoxidase provide a sensitive and specific test for vasculitic syndromes, including Wegener's granulomatosis, microscopic polyarteritis, classic polyarteritis, the Churg-Strauss syndrome, and vasculitis associated with glomerulonephritis.[5] The use of solid phase assays to detect antiserine protease III antibodies or antimyeloperoxidase antibodies has improved the sensitivity of antineutrophil cytoplasmic antibodies testing and allowed accurate measurements of disease activity.[7] The presence of antineutrophil cytoplasmic antibodies in pulmonary renal vasculitis syndromes is well described[4-6]; in addition, antineutrophil cytoplasmic antibodies have been described in patients with idiopathic pulmonary fibrosis.[8] To our knowledge they have not been reported in the context of idiopathic pulmonary haemorrhage.

An unusual feature of the antineutrophil cytoplasmic antibodies in this case is that they were directed against myeloperoxidase, despite producing a cytoplasmic pattern on the indirect immunofluorescence on ethanol fixed cells. No other indirect antigens could be detected by ELISA (alpha granule, anti-29 kDa). In contrast to a previous study,[5] this patient had only IgG ANCA, with virtually no IgM ANCA. The disease had been present for many years and possibly production of the antibodies had switched from IgM to IgG. Indirect immunofluorescence showed no IgM ANCA at the time IgG became positive and the titre did not rise significantly during the course of the illness.

We suggest that ANCA tests should be performed in all patients with acute or chronic pulmonary haemorrhage. Chronic pulmonary haemorrhage, often regarded as diagnostic of idiopathic pulmonary haemosiderosis, may in fact be an occult vasculitis and this has major implications for treatment: evidence of vasculitis would merit treatment with cyclophosphamide and corticosteroids, as recommended by Fauci *et al.*[10]

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Extrinsic allergic alveolitis caused by goose feathers in a duvet

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Abstract

A patient with extrinsic allergic alveolitis had precipitating antibodies to many avian antigens. A duvet containing goose feathers proved to be the source of antigenic material.

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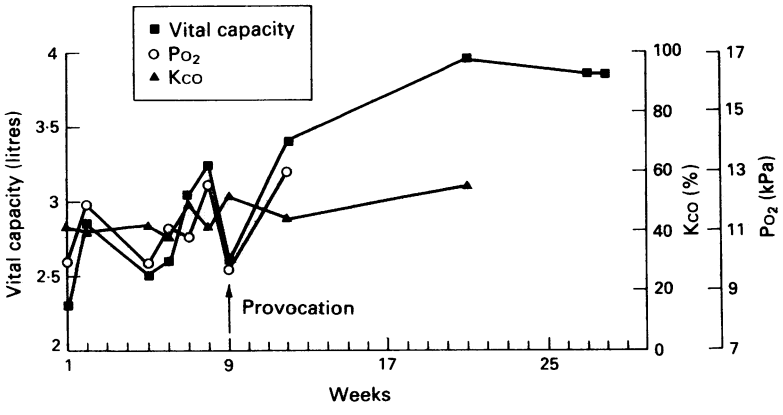
Extrinsic allergic alveolitis is a well known disease caused by inhalation of organic dusts or of inorganic chemicals, leading to bronchoalveolar inflammation. Birds are a common cause and reactions to antigens from pigeons, budgerigars, hens, parrots, canaries, and turkeys have been reported. We describe a case of extrinsic allergic alveolitis caused by goose feathers in a duvet.



Results of lung function tests.

Case report

A 31 year old, previously healthy, non-smoking woman was admitted to hospital with increasing shortness of breath, purulent sputum, and fever. Her complaints had started three weeks previously and had not been improved by erythromycin. She had lost 4 kg. She had no previous history of allergy, occupational exposure to organic or inorganic dusts, or respiratory tract infection. She kept a cat.

A chest radiograph showed a reticulonodular pattern, predominantly in the lower zone. Her erythrocyte sedimentation rate was 29 mm in the first hour (normal <10 mm); angiotensin converting enzyme activity was 85 (normal <50) IU. No other biochemical values were abnormal. Lung function tests showed a vital capacity of 2·3 (normal 3·93) l, an FEV_1 of 1·7 l, a gas transfer coefficient (Kco) of 41%, and hypoxaemia worsening during exercise (arterial oxygen tension 10·0 kPa at rest, 7·5 kPa after cycle ergometer testing with a work load of 13·2 kJ). Specific lung compliance was reduced to 0·28 (expected 0·7–1·1) kPa^{-1}. Bronchoalveolar lavage was performed on day 2, which showed lymphocytosis, with an increased number of T lymphocytes, and a low CD4:CD8 ratio (table). The immunoglobulin: albumin ratios in the lavage fluid supernatant, including IgM:albumin, were increased. These results were consistent with extrinsic allergic alveolitis; a detailed history, however, indicated no possible antigen.

The patient improved spontaneously in hospital, becoming afebrile after seven days, and improvements were seen in the measurements made from a second bronchoalveolar lavage, performed after nine days in hospital (table). She was discharged, and went to stay with her parents, where she continued to improve (figure). Tests for precipitating antibodies against pigeon, budgerigar, canary, and parrot antigens then proved to be positive. A renewed search of the patient's home revealed only a duvet and a pillow, containing nothing but goose feathers (confirmed by the manufacturer) as a possible source of antigenic material. The patient had used the duvet for four years. Retrospectively, the precipitating antibodies against goose antigens proved to be strongly