Anti-basement membrane antibody disease with severe pulmonary haemorrhage and normal renal function

A Tobler, E Schürch, H J Altermatt, V Im Hof

Abstract
A case of anti-basement membrane disease with severe pulmonary haemorrhage and normal renal function is reported.

The histological appearance of the lesion previously described as miliary pulmonary carcinoid tumour with amyloid is identical to that of metastatic medullary carcinoma of the thyroid. This tumour may present with symptoms of the carcinoid syndrome and pulmonary metastases are recognised in disseminated disease. Medullary carcinoma of the thyroid contains calcitonin but so may bronchial carcinoid, and both lesions may contain amyloid.

Medullary carcinoma accounts for about 10% of thyroid tumours and the course of disease is variable. About a quarter of cases are familial. Inherited as an autosomal dominant condition, it may form part of the multiple endocrine neoplasia syndrome type 2. A marfanoid habitus, myopathy, and colonic diverticulosis have been associated with the type 2b variant of this syndrome. Even in cases that are apparently sporadic (probably because gene expression is variable) 10–15% of cases have the familial multiple endocrine neoplasia syndrome. Bilateral tumour and C cell hyperplasia in the thyroid gland may indicate familial disease and screening of relatives by means of stimulated calcitonin measurement may allow early detection and curative surgery. The relatives of our patient are currently undergoing screening. We believe that the patient reported by Skinner and Ewen may have had medullary carcinoma of the thyroid. Multifocal bronchial carcinoid should not be accepted as a primary lung lesion without first excluding metastatic medullary carcinoma of the thyroid.


In 1919 Goodpasture described a syndrome of glomerulonephritis and pulmonary haemorrhage. A century later both manifestations were shown to be induced by circulating autoantibodies that reacted with alveolar and glomerular basement membranes. We present a case with severe pulmonary haemorrhage, mediated by anti-basement membrane antibody in which renal function was normal.

Case report
A previously healthy 20 year old cigarette smoking farmer was referred complaining of dyspnoea and progressive haemoptysis of four days' duration after accidental exposure to fumes of fungicides containing metalaxyl (8%) and mancozeb (64%). He was pale, weak, sweating, and febrile (38.5°C). His pulse rate was 104/min, blood pressure 110/50 mm Hg, and respiratory rate 26/min. A chest radiograph showed diffuse fluffy infiltrates predominantly in the lower lobes. The erythrocyte sedimentation rate was 80 mm in one...
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hour, and he had normochromic, normocytic anaemia (haemoglobin 7-1 g/dl), a white blood cell count of 9-2 × 10^9/l, and a normal platelet count. Clotting studies gave normal results. The urine sediment, results of urine electrophoresis, and creatinine clearance (113 ml/min/1-73 m²) were all normal. A stained sputum smear showed no bacteria but contained abundant erythrocytes and haemosiderin laden macrophages. The arterial oxygen tension (PaO₂) while he was breathing air was 3-7 (normal 10-1-11-8) kPa, oxygen saturation 53%, carbon dioxide tension (PaCO₂) 4-3 (normal 4-8-6-1) kPa; pH 7-47. Antibodies to cell nuclei, DNA, and neutrophil cytoplasm were not detectable. No antibodies to common viruses, Q fever agent, mycoplasmas, chlamydia, or human immunodeficiency virus were detected. The indirect immunofluorescence test for antibodies to lung basement membrane showed a raised titre of 1:128. A titre 1:20 of anti-glomerular basement membrane antibody was measured by the enzyme linked immunosorbent assay and confirmed by immunoblotting (fig 1). HLA tissue typing showed the patient to be HLA-DR2.

Initial treatment included oxygen and daily intravenous methylprednisolone (1 g) for three days followed by oral prednisone 50 mg daily. On days 2, 3, and 4 plasmapheresis was performed. The patient recovered rapidly. On day 6 a chest radiograph showed minimal patchy opacities and the PaO₂ was 8-2 kPa in air. At that time a transbronchial lung biopsy and a renal biopsy were performed. The lung biopsy specimen showed extravasation of red blood cells and haemosiderin laden macrophages. The renal biopsy specimen issue was normal. Examination of the lung and kidney specimens by direct immunofluorescence showed linear deposits of IgG and C₃ along the alveolar basement membrane and linear deposits of IgG, IgM, and C₃ along the glomerular basement membrane (fig 2). The patient was discharged on oral prednisone, 15 mg daily. Four months later the chest radiograph, blood gases, renal function, and haemoglobin concentration were normal. After 12 months the patient remains well and has discontinued treatment.

![Immunoblot showing anti-glomerular basement membrane antibodies in the patient's serum. Lanes 1-4: serum from healthy individuals (negative control); lanes 5 and 6: serum from the patient, diluted 1:10 and 1:20 respectively; lanes 7 and 8: positive control. In Goodpasture's syndrome bands are visible at 50, 28, and 26 kD (arrows). The immunoblotting was performed as follows. Human glomerular basement membranes were obtained from kidneys at necropsy and solubilised with collagenase. Separation was by SDS polyacrylamide gel electrophoresis. The gel was blotted on to a nitrocellulose filter, which was cut into strips (Nos 1-8) and incubated with dilutions of serum.](http://thorax.bmj.com/)

**Figure 1** Immunoblot showing anti-glomerular basement membrane antibodies in the patient's serum. Lanes 1-4: serum from healthy individuals (negative control); lanes 5 and 6: serum from the patient, diluted 1:10 and 1:20 respectively; lanes 7 and 8: positive control. In Goodpasture's syndrome bands are visible at 50, 28, and 26 kD (arrows). The immunoblotting was performed as follows. Human glomerular basement membranes were obtained from kidneys at necropsy and solubilised with collagenase. Separation was by SDS polyacrylamide gel electrophoresis. The gel was blotted on to a nitrocellulose filter, which was cut into strips (Nos 1-8) and incubated with dilutions of serum.

Discussion

Goodpasture's syndrome consists of pulmonary haemorrhage and glomerulonephritis. The discovery of antibodies deposited on alveolar and glomerular basement membranes allowed a more precise characterisation of this disorder. Our patient showed the rare combination of severe pulmonary haemorrhage mediated by anti-basement membrane antibodies and normal renal function. Renal failure did not occur in the year of follow up. Most patients with anti-basement membrane antibody disease develop glomerulonephritis that progresses rapidly to end stage renal failure.³ Up to 80% of these patients also have affected lungs. Cases in which the lung disease predominates are rare, with only a few reports of isolated anti-basement membrane antibody induced pulmonary haemorrhage and normal
renal function at the time of diagnosis. Severe renal failure may develop in some patients, but others improve and no renal dysfunction occurs during follow up.

The reason why some patients are more susceptible to lung than to renal disease is not clear. Inhaled agents may play a part, among them insecticides and herbicides. The fungicides inhaled by our patient have not been reported to induce anti-basement membrane antibody disease, but cigarette smoking is associated with pulmonary manifestations of the disease. In animals inhalation of petrol induces lesions in the alveolar basement membrane, allowing circulating anti-basement membrane antibodies to gain access. Thus increased capillary permeability may be essential for damage to occur. Our patient was a cigarette smoker and was exposed to fumes of fungicides, both of which might have been contributory factors. The unusual susceptibility of a few individuals to widely used exogenous agents suggests a genetically determined background for the development of anti-basement membrane antibody disease. This is supported by the association of the HLA antigen DR2, which our patient possessed, with the disease. 

Treatment regimens consist of immunosuppression with or without plasmapheresis. The outcome in patients treated with plasmapheresis is slightly better; but the initial degree of the renal disease is more important for the prognosis than the type of treatment received. Combined cytotoxic drugs and plasmapheresis also shorten the time needed for clearance of antibodies and improve the outcome in patients with lung haemorrhage and in those not dependent on dialysis.

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Antimyeloperoxidase antibodies in the Churg-Strauss syndrome

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Abstract

Antibodies to myeloperoxidase were detected in the serum of three patients with the Churg-Strauss syndrome.

The Churg-Strauss syndrome, a rare multisystem disorder thought to be related to the systemic necrotising vasculitides, is characterised by hypereosinophilia, systemic vasculitis, asthma, and allergic rhinitis. Extravascular granulomas are frequently found but are absent in many cases. Antineutrophil cytoplasmic autoantibodies (ANCA or ACPA) have been described recently in patients with Wegener’s granulomatosis and microscopic polyarteritis. These antibodies are directed against a 29 kD glycoprotein with serine protease activity derived from the azurophil granules of the neutrophil, probably proteinase-3. A characteristic granular pattern of staining of the cytoplasm of ethanol fixed granulocytes occurs (c-ANCA). Other staining patterns, however, have also been recognised—in particular, a perinuclear pattern. It has been shown that a substantial number of serum samples producing a perinuclear pattern have antibodies to human leukocyte elastase and/or myeloperoxidase, both lysosomal enzymes. In this report we describe the occurrence of myeloperoxidase ANCA in three consecutive patients with the Churg-Strauss syndrome.

Case reports

PATIENT I

A 24 year old man presented in 1984 with asthma, rhinitis, and loss of weight. Treatment was started with corticosteroids. While the dose was being reduced severe dyspnoea developed followed by arthralgia, myalgia, episcleritis, fever, and mononeuritis multi-
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