Case Report

Goodpasture’s syndrome with normal renal function

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Introduction

At the height of the influenza pandemic of 1919, Ernest W. Goodpasture described the post-mortem findings of an 18-year-old man who developed progressive haemoptysis and renal failure. Subsequently the eponym Goodpasture’s syndrome has been applied to patients with a combination of pulmonary haemorrhage and glomerulonephritis, particularly where the disease process involves the presence of autoantibodies directed against the glomerular basement membrane. It is an uncommon condition and untreated is often fatal, due to uncontrollable pulmonary haemorrhage or rapidly progressive renal failure. Here we present a more rarely reported case of antiglomerular basement membrane (anti-GBM) antibody-mediated disease in which urinalysis was normal at presentation and where renal function has remained normal.

Case Report

A 22-year-old male student presented with a 4-month history of lethargy, dyspnoea and haemoptysis. The haemoptysis was exacerbated by cigarette smoking. A chest radiograph showed bilateral mid- and lower-zone consolidation and he was treated with antibiotics for a presumed chest infection. The patient’s symptoms improved following treatment but he remained dyspnoeic, with poor exercise tolerance, and he was found to be anaemic with a haemoglobin level of 8.3 g/dl. The patient was referred to the medical outpatient clinic. Clinical examination and urinalysis were normal. A further chest radiograph was normal and sputum microscopy and culture was negative for pathogenic organisms including Mycobacteria and Legionella species. He had an anaemia of 9.1 g/dl with a hypochromic microcytic picture, and a white count of 8.3 x 10^9/l and platelets 442 x 10^9/l, reticulocyte count 11%. Erythrocyte sedimentation rate was 3 mm in the first hour and C-reactive protein 5 mg/l. Urea, creatinine and electrolytes were normal. A viral and atypical pneumonia screen showed raised titres for Mycoplasma pneumoniae (1:64), influenza A (titre 1:125), influenza B (1:32), but serum immunoglobulins and electrophoresis were normal. An autoantibody screen including ANA and ANCA was negative. Lymphocyte subset examination suggested a slight reduction in CD4 and B cells. Anti-GBM antibody assays performed at that time were reported as slightly raised (8 arbitrary antibody units (aau) at a dilution of 1 in 100, i.e. negative (<10 aau), though positive 27 aau at 1 in 10) [1].

At a week’s follow up the haemoglobin had fallen to 7.5 g/dl. He was admitted to hospital and transfused with 4 units of blood. Repeat anti-GBM assays were performed and results awaited. Creatinine clearance calculated from 24-h urine collection was 100.4 ml/min, and urinary excretion of protein was less than 0.2 g/24 h. Lung function studies corrected for haemoglobin were FEV1 3.72 l (80% of reference), FVC 4.15 l (75% of reference), FEV1/FVC 90%, TlCO 8.09 mmol/min/kPa (64% of reference), Kco 1.56. Bronchoscopy with transbronchial biopsy was performed and samples sent for laboratory examination. There was a symptomatic improvement with no further haemoptysis and the patient was discharged.

A week later, following an episode of minor exposure to diesel fumes, he presented again with haemoptysis, malaise and dyspnoea. He was pyrexial 38.5°C, tachycardic 96 b.p.m., and dyspnoeic, but examination was otherwise unremarkable. Urinalysis on this occasion revealed microscopic haematuria and proteinuria. Results of blood tests were as follows: WCC 10.6 x 10^9/l, Hb 11.6 g/dl, platelets 240 x 10^9/l, Na 135 mmol/l, K 3.7 mmol/l, urea 4.5, creatinine 101 μmol/l. Arterial PO2 was 7.28 kPa (FjO2 = 21%), with a PCO2 of 4.63 kPa. A chest radiograph revealed alveolar shadowing throughout the left lung field (Fig. 1). Pulmonary function tests were consistent with pulmonary haemorrhage, TlCO at 10.1 mmol/min/kPa, and an increased Kco 2.4. His spirometry...
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had deteriorated FEV₁ 2.5 l, FVC 3.4 l, FEV₁/FVC 74%. By this time results of his previous anti-GBM assay were available and these were positive with increased titres (11 aau at 1 in 100, 62 aau at 1 in 10). Repeat samples showed falling titres of 4 aau at 1 in 100, and 21 aau at 1 in 10. Immunofluorescence of lung biopsy specimens were also available and these showed linear deposition of IgG and C3 in the alveoli (Fig. 2).

The patient was commenced on a 5-day course of plasmapheresis and given three boluses of i.v. methylprednisolone 1g and a single dose of cyclophosphamide at 600 mg/m² with Mesna at 360 mg/m². Thereafter he received 60 mg oral prednisolone. The patient’s haemoglobin during this period dropped to 6.8g/dl and he was transfused with 4 units of blood. By the 4th session of plasmapheresis repeat anti-GBM antibody titres had fallen below the reference range (1.5 aau at 1 in 100, 4 aau at 1 in 10). After 7 days the haemoptysis had resolved, chest radiograph showed significant improvement, and arterial oxygen tension had risen to 10.09 kPa (FiO₂ = 21%). His serum creatinine was 82 μmol/l and 24-h urinary excretion of protein was measured at 0.44g. The patient was discharged on the 11th day. His tissue type was later found to be HLA DR15 [2].

At 2 months follow-up, he remains well, receiving 20 mg prednisolone daily and a monthly dose of cyclophosphamide 300 mg/m². He has had no further haemoptysis and his renal function has remained normal. Anti-GBM antibody titres are shown in Fig. 3.

Discussion

Goodpasture’s syndrome is rare, and its incidence has been estimated at 0.5 new cases per million per year in the UK. It has a poor prognosis despite modern treatment methods, with a high mortality of 11%, and high morbidity, where 60% of patients may expect to become dialysis dependent [2]. Most cases of anti-GBM antibody-mediated disease are characterized by both pulmonary and renal involvement and often there is extensive and progressive glomerular disease.
The case presented here shows some typical features of Goodpasture's syndrome, since patients are more often young, male and in the presence of pulmonary disease, likely to smoke cigarettes [3]. In common with previous reports of Goodpasture's syndrome, there is a history of chest infection and also there is evidence of deterioration following exposure to hydrocarbon fumes [4]. This patient had HLA DR2, which has been found in 88% of cases of anti-GBM antibody-mediated disease versus 25–32% in control blood donors [5]. However, our patient's presentation is rare and unusual in that despite florid pulmonary disease there was only very minor renal involvement. That this is unusual is illustrated in Table 1, where in some series urinary abnormalities are present in up to 100% of cases. That such cases have occurred is not widely known though similar cases have been reported [2–4,6–10].

This patient's history highlights the important point that physicians need to consider the diagnosis of anti-GBM antibody-mediated disease in patients with pulmonary haemorrhage or anaemia, even when, as in this patient, the initial urinalysis is clear and renal function is normal. Moreover this case raises the question of whether this and similar cases represent a distinct form of anti-GBM antibody-mediated disease, or is simply the same disease in an earlier stage.

It has long been known that in many cases of anti-GBM antibody-mediated disease, pulmonary haemorrhage precedes overt renal disease by some weeks, and in a few cases by years [6]. Pulmonary manifestations appear to occur before renal involvement in most cases, with 82–94% of patients initially presenting with haemoptysis, of which 50–80% then go on to develop glomerulonephritis [5]. These figures therefore suggest that although cases of predominantly renal disease do occur, for a majority of cases the disease process affects the lungs first, then the kidneys. It is therefore possible, as has been suggested previously [10], that the absence of significant renal involvement may be simply due to early detection. This might be explained by improved anti-GBM antibody assays, and with earlier treatment the progression of any renal disease may be halted or even reversed, as demonstrated by one case in which on follow-up renal biopsy the deposits of anti-GBM antibodies had disappeared [10].

The history of this patient supports proposed respiratory aetiologies for Goodpasture's syndrome. In addition to his cigarette smoking and hydrocarbon fume exposure, his history of respiratory-tract infection and influenza-like illness is shared with 20–61% of cases of anti-GBM antibody-mediated disease [5]. This patient was also found to have a raised titre for influenza A, and serologically proven Influenza A2 infection has previously been reported in association with Goodpasture's syndrome [11].

Recent advances in understanding the pathogenesis of Goodpasture's syndrome further suggest that the disease process may begin in the lungs. The 'Goodpasture antigen' has been localized and characterized. It is now known to be a component of the NC1 domain of type IV collagen, which forms the backbone of basement membrane. More specifically the epitope is found on the α3 chain of type IV collagen and forms a 28-kDa monomeric subunit [α3(IV) NC1]. This α3 chain has been mapped to chromosome 2 [12]. The NC1 domain of type IV collagen has been found in the basement membranes of glomeruli, renal tubules, lung, placenta and small intestine, but the preference of anti-GBM antibodies for glomerular and alveolar basement membrane appears to be due to an increased
accessibility of epitopes and a greater expression of the \( \alpha 3 \) chain in these tissues [13]. Under normal circumstances alveolar capillaries are continuous, and unlike glomerular capillaries are not fenestrated; thus, large, charged molecules such as immunoglobulin are excluded. It is therefore only after damage to the lung, for example due to cigarette smoke or infection that alveolar capillaries become more porous and the alveolar Goodpasture antigen becomes exposed. It is perhaps this unusual exposure in the presence of infection or damage, which in genetically susceptible individuals (i.e., HLA DR2), triggers the autoimmune process.

This deeper understanding of the pathogenesis of Goodpasture’s syndrome appears to provide a number of pathological mechanisms by which variants of anti-GBM disease might arise. Recent studies have revealed that whilst antibodies to the \( \alpha 3(IV) \) NC1 epitope are found universally in cases of anti-GBM disease, additional limited reactivity to other epitopes, i.e., \( \alpha 1(IV) \) NC1 and \( \alpha 4(IV) \) NC1, is found in a minority of cases (15%). Moreover this non-\( \alpha 3(IV) \) NC1 reactivity was found most frequently in patients with anti-GBM antibodies and glomerulonephritis alone [14]. Unfortunately it has not been possible to determine the specific epitopes to which the anti-GBM antibodies present in this case were reacting to, but the possibility remains that the presence of antibodies to epitopes other than \( \alpha 3(IV) \) NC1 may lead to differing presentations of anti-GBM disease.

Another mechanism by which anti-GBM antibodies may vary between patients is the nature of the immunoglobulin present. Goodpasture’s syndrome has characteristically been described as being due to IgG antibodies, although a case involving IgA has been previously reported [15]. The subtype of IgG antibody involved may also vary, and previous studies have suggested that a majority of cases of Goodpasture’s syndrome involve only subtypes IgG1 and IgG4 [16,17]. Using a method modified from Falconer et al. [18], IgG subclass analysis was performed on samples from this patient and results indeed showed a predominance of IgG1 and IgG4 activity, though some IgG2 and IgG3 activity was noted (IgG1 > IgG4 > IgG2 > IgG3). Different IgG subclasses have different biological properties, i.e., IgG1, unlike IgG4, can fix complement and bind macrophages, and it seems possible that different proportions of each of the IgG subtypes may result in a variety of clinical presentation and disease progression.

This case has illustrated the need to consider anti-GBM antibody-mediated disease in patients who present with haemoptysis or anaemia despite normal renal function and urinalysis. It has shown the successful use of transbronchial biopsy to diagnose anti-GBM antibody-mediated disease and exclude concurrent infection prior to immunosuppression. It seems plausible that anti-GBM antibody mediated disease with normal renal function may represent an early form of the complete Goodpasture syndrome, and it appears that it is effectively treated with plasmapheresis and immunosuppression.

References


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