Renal vasculitis in antiglomerular basement antibody-positive Goodpasture disease

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Introduction

Goodpasture disease is a rare cause of acute renal failure and classically presents with pulmonary haemorrhage, oliguric renal failure, and crescentic glomerulonephritis with in vivo deposition of antiglomerular basement (anti-GBM) antibody. Anti-GBM antibody is also detected in the serum and is a highly specific and sensitive disease marker [1]. Patients with systemic vasculitis and circulating antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis may clinically present in a similar way, but on renal biopsy antibody deposition is not detected. Renal vasculitis is usually seen in association with ANCA positivity [2]. We describe an ANCA-negative patient who had pulmonary haemorrhage, granulomatous crescentic nephritis, necrotizing renal vasculitis, and circulating anti-GBM antibody in the absence of glomerular anti-GBM deposition.

Case report

A 72-year-old caucasian male was admitted with 1 week of sore throat and aching joints. He had noticed a reduction in his urine volume in that time and for the 24 h before admission had not passed urine at all. He had been taking ciprofloxacin for 3 days. His only maintenance medication was bendrofluazide for hypertension and Nylax (bisocoly, phenolphthalein and senna) for constipation. He had given up smoking 10 years before. On admission, he was pyrexial and clinically uraemic; BP 160/100. Immediate investigations demonstrated a left lower-zone consolidation on chest X-ray, serum creatinine 945 μmol/l, haemoglobin 10.6 g/dl, white count 14.5 × 10^9/l, and CRP 267 mg/l. ANCA was negative, as were myeloperoxidase and proteinase 3 ELISAS. Blood anti-GBM antibody was not requested initially. There was blood and protein in his urine. A renal ultrasound was normal. He was haemodialysed and the following day underwent a percutaneous renal biopsy. Eleven glomeruli were present in the biopsy. All showed florid cellular or fibrocellular crescents. There was extensive necrosis of the glomerular tufts and only in an occasional glomerulus could residual capillary basement membrane be identified. In approximately 70% of glomeruli, there was partial destruction of Bowman’s capsule with a marked histiocytic and giant-cell granulomatous response surrounding the glomerulus. An extensive vasculitis was also present involving small arteries and arterioles (Figure 1). On immunofluorescence all six glomeruli present showed patchy staining for complement and fibrinogen within the crescents and blood vessels. No immunoglobulin deposition could be identified. As it was not possible to determine whether the lack of staining in the glomeruli was due to genuine negative anti-GBM staining or merely the absence of identifiable basement membrane, immunoperoxidase was performed on the original paraffin-embedded block. Only an occasional small strip of fragmented basement membrane could be identified within the crescents. This was weakly positive for C1q and C3, but negative for immunoglobulins. Fibrin and complement were once again present in crescents and blood vessels.

No glomeruli could be identified on electron microscopy. The patient was initially treated with IV cefuroxime, methylprednisolone, and cyclophosphamide, and converted to oral therapy after 1 week. His clinical condition improved rapidly, though renal function did not return. Three weeks after admission he became increasingly dyspnoeic and suffered massive haemoptyses. A chest X-ray was compatible with pulmonary haemorrhage (Figure 2). Anti-GBM antibody titre was now found to be strongly positive. Intravenous immunosuppression was restarted and plasmapheresis commenced. The pulmonary haemorrhage eventually subsided after a week, but he was left with considerable pulmonary fibrosis and recurrent...
Vasculitis in Goodpasture disease

Fig. 1. Crescent formation and granulomatous reaction. The adjacent small artery shows a vasculitis with destruction of the elastic laminae. (Modified Jones Silver stain ×600).

Fig. 2. Chest X-ray at the time of massive haemoptysis and immediately preceding plasma exchange.

chest infections. Serial testing for ANCA remained negative and the anti-GBM titre progressively fell, becoming negative 3 months after admission. At no time was there clinical evidence of systemic vasculitis. After a further 6 months, he developed end-stage respiratory failure and haemodialysis was withdrawn.

Permission for post-mortem was refused.

Discussion

This patient with the pulmonary-renal syndrome was extremely unusual. The clinical presentation with a very short prodrome and severe pulmonary haemorrhage favours classical Goodpasture disease. This diagnosis is strongly supported by the presence of anti-GBM antibodies in his serum, but it was surprising that no immunoglobulin deposition could be identified on immunofluorescence or immunoperoxidase in the renal biopsy. We believe, however, that this can be explained by the severity of the destruction of the glomerular basement membrane.

The renal biopsy also showed an extensive vasculitis of small arteries and arterioles, and the glomeruli were replaced by non-caseating granulomata of the type seen in Wegener’s vasculitis [3]. The lack of immunoglobulins in the glomeruli would be in keeping with this condition, and ANCA-negative Wegener’s vasculitis, though rare, is well described [4]. An alternative explanation of this patient’s illness could, therefore, be a primary vasculitic condition with anti-GBM antibodies formed as an epiphenomenon following destruction of glomerulus and glomerular basement membrane. However, our patient gave one of the highest optical density readings we have seen in 7 years of routine anti-GBM screening using a commercial ELISA kit,
which uses the M2 peptide, derived from the non-collagenous (NC) globular domain of collagen type IV as antigen and detects IgG antibody (Bio-Diagnostics Ltd, Upton-upon-Severn, UK).

We test sera from cases of acute rapidly progressive glomerulonephritis from a large area of the South-West of England and less than 1% prove to be unequivocally positive. This method is highly specific for anti-GBM disease in our hands. Typical optical density readings for healthy blood donors, patients with biopsy-proven anti-GBM disease, and the very strong positive kit control sample are less than 0.2, greater than 0.2 (but typically greater than 0.7) and greater than 1.0 respectively. In our patient pre-plasma exchange, two samples were strongly anti-GBM positive, giving optical density readings of 1.133 and 1.011 (94% and 97% respectively of the kit positive control run each time).

The same samples tested negative for ANCA by indirect immunofluorescence with human neutrophils as substrate [4]. Protinase 3 (Shield Diagnostics, Dundee, Scotland) and myeloperoxidase (in house method, commercial source MPO: Calbiochem-Nova Biochem) ELISAs were also negative. Both ELISA assays detect IgG antibody. All these results were independently confirmed in another laboratory (see Acknowledgements). We believe, therefore, that our patient had Goodpasture disease even though we have never before seen positive circulating anti-GBM antibodies without biopsy-proven anti-GBM disease. However, two similar cases of anti-GBM disease with vasculitis have been reported before, though the ANCA status of these patients is unknown [5]. Another patient with histological vasculitis and circulating antibodies to GBM was reported in a series of rapidly progressive glomerulonephritis, but in this case antineutrophil cytoplasmic antibodies were present and no other details were given [6].

Thus although the existence of vasculitis and anti-GBM disease has been previously described, the present report is, as far as we are aware, the first of an ANCA-negative vasculitis and Goodpasture disease in the same patient. The pathogenesis of the vasculitis in these cases is unknown.

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References


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