Case Report

Recurrence of anti-GBM disease 8 years after renal transplantation

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Introduction

Anti-glomerular basement membrane (GBM) disease is a disorder characterized by antibodies against an epitope of type IV collagen found on the GBM. The major clinical sequela is rapidly progressive glomerulonephritis, which may be accompanied by pulmonary haemorrhage (Goodpasture’s syndrome). Glomerulonephritis secondary to anti-GBM disease frequently progresses to end-stage renal disease (ESRD) in the subset of patients who present with markedly impaired renal function. Renal transplantation is performed for ESRD due to anti-GBM disease, although most centres delay transplantation until patients are anti-GBM antibody negative for at least 12 months. Although early case series showed frequent recurrence in the allograft [1], modern therapeutic approaches have made recurrent disease very rare, and only four cases have been reported [2–5]. The effect of therapy for recurrent allograft disease is not well described. We report a case of recurrent anti-GBM disease in a renal allograft with successful salvage of the allograft.

Case

A 48-year-old female renal transplant recipient was admitted in December 2001 with acute renal failure after presenting with a 4-day history of weakness, easy fatigability and anorexia. There was no history of volume depletion or nephrotoxins and she denied any urinary symptoms, sore throat, cough, haemoptysis, oral ulcers, rash or arthritis.

Her past medical history was significant for systemic lupus erythematosus (SLE) diagnosed in 1988 when she presented with fever, rash, polyarthritis and anasarca. Investigations revealed nephrotic range proteinuria, positive ANA, positive anti-double-stranded (ds) DNA and low complements. Renal biopsy showed focal proliferative glomerulonephritis and she was initially treated with pulse methylprednisolone and cyclophosphamide. She was treated subsequently with azathioprine in addition to oral prednisone. Her serum creatinine was 80 μmol/l in December 1990. She presented with fever, anorexia, and myalgias in January 1991. Investigations confirmed acute renal failure with serum creatinine of 1214 μmol/l. Renal biopsy showed severe crescentic glomerulonephritis with characteristic strong linear staining of IgG along the GBM by immunofluorescence and positive serum anti-GBM antibody test. A few days after admission, she developed a pulmonary haemorrhage and required intubation and mechanical ventilation. She received plasma exchange, pulse steroids and cyclophosphamide. She recovered pulmonary function but her renal function did not improve and she was initiated on long-term peritoneal dialysis for ESRD. Over the next 2 years, her disease was clinically quiescent and serological investigations showed persistently negative anti-GBM antibody. She received a human leukocyte antigen (HLA)-identical living related renal transplant from her sister. Her post-operative course was uncomplicated. She was maintained on cyclosporine and prednisone with a baseline creatinine of 140–160 μmol/l. Other history was significant for recurrent graft pyelonephritis, renal cell carcinoma involving the left native kidney requiring nephrectomy in February 2001, and a remote history of ulcerative colitis.

On examination, the patient was afebrile, blood pressure was 130/70 mmHg with no postural change, respiratory rate was 20/min and oxygen saturation was 98% on room air. Jugular venous pressure was normal. There was no peripheral oedema. Respiratory examination was within normal limits and there was...
no graft tenderness. There was no rash and no active joints.

Urine dip showed moderate blood and trace protein, and microscopy revealed 2–3 red blood cells (RBCs) and 3–5 white blood cells (WBCs) per high power field. Haematology revealed haemoglobin 94 g/l, WBC 9.5 × 10^9/ml and platelet count 334 × 10^9/ml. Biochemistry revealed sodium 135 mmol/l, potassium 4.8 mmol/l, chloride 101 mmol/l, bicarbonate 21 mmol/l, creatinine 405 μmol/l, urea 22.9 mmol/l, calcium 2.6 mmol/l and magnesium 0.87 mmol/l. Transplant ultrasound demonstrated no evidence of vascular compromise and no obstruction to urinary flow. Urine culture did not reveal any growth. Serology showed ANA 1:160, anti-dsDNA negative and positive anti-GBM antibody. Serum complement components C3 and C4 were normal.

A renal biopsy was performed the day following admission and showed 12 glomeruli, eight of which had large cellular crescents, with segmental fibrinoid necrosis and disruption of GBM, acute tubular necrosis and a diffuse mixed interstitial inflammatory infiltrate. Vessels showed mild hyaline arteriosclerosis and there was vasculitis. Immunofluorescence microscopy revealed 1+ linear staining for IgG along the GBM, trace staining for IgM, 1+ for κ and λ and negative for IgA (Figure 1). Electron microscopy showed no deposits and segmental effacement of foot processes.

The patient was treated with i.v. methylprednisolone 1 g/day for 3 days, followed by oral prednisone 1 mg/kg, oral cyclophosphamide 2 mg/kg and plasma exchange for 5 days. She responded well to treatment, did not require dialysis, and she was discharged from the hospital after 11 days. Serum creatinine at the time of discharge was 218 μmol/l. At 11 months follow-up, her creatinine is 214 μmol/l. She is currently maintained on cyclosporine 75 mg bid, cyclophosphamide 100 mg od, and prednisone 7.5 mg od.

Discussion

We have reported a patient who experienced two very rare immunological entities: anti-GBM disease superimposed on SLE, and recurrent anti-GBM disease in a renal allograft. Anti-GBM antibody disease has been reported to co-exist with pauci-immune anti-neutrophil cytoplasmic autoantibody (ANCA)-positive glomerulonephritis [6], membranous glomerulopathy, membranoproliferative glomerulonephritis and IgA nephropathy. Anti-GBM antibody disease is very rare among patients with SLE, with only one case reported [7]. Our patient initially developed anti-GBM antibody disease, pulmonary haemorrhage and rapidly progressive glomerulonephritis (Goodpasture’s syndrome) while on prednisone and azathioprine for SLE. One can postulate that the GBM injury

Fig. 1. Immunofluorescence for IgG in the transplant kidney showing weak linear staining along the glomerular basement membranes. Original magnification, ×250.
Recurrence of anti-GBM disease 8 years after transplantation

Table 1. Summary of case reports of recurrent anti-GBM antibody disease after transplantation

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/gender</th>
<th>Time from transplant to recurrence</th>
<th>Precipitant</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beleil et al. (1973)</td>
<td>31/M</td>
<td>1: 6 months</td>
<td>Unknown</td>
<td>1: steroids</td>
<td>Both grafts lost</td>
</tr>
<tr>
<td>Almquist et al. (1981)</td>
<td>48/F</td>
<td>2: 6 months</td>
<td>Identical twin transplant, no immunosuppression</td>
<td>2: not stated</td>
<td>Graft salvaged (3 year follow-up)</td>
</tr>
<tr>
<td>Trpkov et al. (1998)</td>
<td>41/M</td>
<td>12 years</td>
<td>Possible de novo IgA nephropathy</td>
<td>Plasmapheresis, steroids, i.v.</td>
<td>Graft lost</td>
</tr>
<tr>
<td>Fonck et al. (1998)</td>
<td>33/F</td>
<td>5 years</td>
<td>Withdrawal of cyclophosphamide</td>
<td>Plasma exchange, pulse steroids, oral cyclophosphamide</td>
<td>Graft salvaged (11 months follow-up)</td>
</tr>
<tr>
<td>Khandelwal et al. (this study)</td>
<td>48/F</td>
<td>8 years</td>
<td>Unknown (see text)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This patient lost two sequential transplants to recurrent anti-GBM antibody disease.

from SLE or subclinical lupus pneumonitis may have precipitated anti-GBM antibody formation and Goodpasture’s syndrome during her disease course in the pre-transplant period.

Recurrent anti-GBM antibody disease in the renal allograft is also very rare, with only four case reports since 1973. Table 1 shows the characteristics of these cases. While precipitating factors were identified in some cases, we can only postulate as to why our patient was predisposed to recurrent disease. She was on relatively low dose immunosuppression given that she had an HLA-identical kidney from her sister, and this may have made her prone to recurrent disease. The patient reported by Almquist et al. [3] also had an HLA-identical graft (identical twin) and it is possible that re-exposure to genetically similar antigen induces anti-GBM antibody production, especially in the context of low dose immunosuppression. Alternatively, we can speculate that the removal of the renal cell carcinoma 10 months earlier could have resulted in re-exposure to previously concealed antigen resulting in recurrent autoimmunity. Pauci-immune crescentic glomerulonephritis, but not anti-GBM disease, has been associated with renal cell carcinoma [8]. Disease occurrence has also been linked to environmental exposure to cigarette smoke, hydrocarbon solvents, organic solvents, herbicides, bacterial and viral infections [9,10]. Our patients did not have exposure to any of these known precipitating factors.

Our patient’s response to therapy is also noteworthy. The low likelihood of acute rejection and a high index of suspicion for recurrent disease led to an early biopsy and subsequent successful therapy with plasma exchange and immunosuppressive therapy using the same protocol as for de novo anti-GBM antibody disease. Early recurrence was treated successfully by Almquist et al. [3] but the patient reported by Fonck et al. [5] lost her graft despite immunosuppressive therapy. The patient reported by Trpkov et al. [4] was treated with both immunosuppressive therapy and plasma exchange, but died 1 month after presentation from gastrointestinal bleeding. Thus, we consider our case to be the first report of successful graft salvage from late recurrent anti-GBM disease with immunosuppressive therapy and plasma exchange.

In conclusion, recurrent anti-GBM antibody disease should be considered as a cause of unexplained graft dysfunction in patients with ESRD due to anti-GBM antibody disease. It is possible that the incidence of recurrent disease is higher with HLA-identical kidneys. Recurrent disease, although rare, can occur at any time after transplantation and should be considered with late graft dysfunction. There is often, but not always, an identifiable precipitating factor. A high index of suspicion is the key for early diagnosis because it has been shown that prompt treatment can salvage the graft.

Conflict of interest statement. None declared.

References


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