Relapse rate and outcome of ANCA-associated small vessel vasculitis after transplantation

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Abstract

Background. Anti-neutrophil cytoplasm antibody-associated systemic vasculitis (AASV) is a rare disease and frequently leads to end-stage renal disease (ESRD). Potentially fatal disease activity can develop after the onset of ESRD or in transplanted patients despite the immunosuppressive effects of uraemia and rejection prophylaxis, respectively, leading to concern that such patients may have greater morbidity and mortality.

Methods. To assess the outcome of patients with AASV following kidney transplantation, a retrospective analysis was performed of nine patients with AASV at our unit who received renal transplants between 1987 and 2000. The renal survival of the patients was compared with a control population who received kidney transplants over the same period for causes other than AASV and diabetes mellitus.

Results. Nine patients with the diagnosis of AASV (five patients with Wegener’s granulomatosis and four with microscopic polyangitis) received eight cadaveric grafts and one live-related graft after a mean of 44 months from the start of dialysis. These patients had a mean age of 49.2 years at time of transplantation and they were followed up for a mean of 62 months post-transplantation. Two patients with Wegener’s granulomatosis suffered a vasculitic relapse affecting the upper respiratory tract at 40 and 50 months post-transplantation, corresponding to a relapse rate of 0.04 per patient per year. The renal transplant function of vasculitis patients compared with 18 non-diabetic control patients who were transplanted at the same time was better in the vasculitis patients at some time points ($P = 0.054$ at 6 months).

Conclusions. There is a substantial relapse rate in the AASV population, especially affecting the upper respiratory tract and with increasing duration of follow-up. Nonetheless, renal transplantation is a good option for the treatment of vasculitis patients and their outcome compares favourably with that of other non-diabetic patients following transplantation.

Keywords: relapse; renal transplantation; vasculitis

Introduction

Anti-neutrophil cytoplasm autoantibodies (ANCA) occur in patients with certain forms of systemic necrotizing vasculitis [1]. ANCA-associated vasculitis is a rare pathology in the general population, with an incidence around 20 per million population per year. Conversely, it is the most common cause of rapidly progressive glomerulonephritis-induced end-stage renal failure (ESRF) despite treatment with immunosuppressive drugs, including cyclophosphamide and steroids [2,3]. The renal survival is between 78 and 58% for patients alive at the end of 10 years and for those dying during follow-up, respectively [4]. For those patients reaching ESRF, transplantation may be an option. However, several studies have shown that systemic vasculitis recurs in ~25% of patients following renal transplantation [5–7]. We report on nine patients with biopsy-proven systemic vasculitis that was associated with ANCA, who rapidly progressed towards ESRF and were submitted to renal transplantation.

Subjects and methods

Records of all patients transplanted at the Queen Elizabeth Hospital since 1985 were reviewed and all patients with the primary diagnosis of vasculitis were selected. Records were evaluated to determine if the diagnosis corresponded with ANCA-associated systemic vasculitis (AASV) as defined by the Chapel Hill Consensus Conference [8]. Clinical data were extracted on these patients, including time from diagnosis to transplantation, survival of the allograft and episodes of acute rejection, current level of renal function, serology at
time of transplantation and present, episodes of vasculitis relapse and how these were managed. The survival of patients and allografts was compared with a control population comprising two controls per patient. The controls comprised the two patients transplanted immediately before and after the patient with vasculitis, providing neither had diabetes mellitus, in which case the next closest patient without diabetes mellitus was selected.

Relapse required the recurrence or new appearance of organ involvement that was attributable to vasculitis. Relapses are classified as severe if they threaten vital organ function, including a reduction in renal function secondary to biopsy-proven active focal necrotizing glomerulonephritis, evidence of pulmonary haemorrhage, threatened vision, significant subglottic or bronchial stenosis, new multifocal lesions on brain magnetic resonance imaging suggestive of vasculitis, mononeuritis multiplex and gastrointestinal haemorrhage or perforation. Relapses are classified as minor when of lesser severity, including epistaxis, crusting, new deafness, active nasal ulceration, mouth ulcers, rash, myalgia, arthralgia and episcleritis.

Bartlett’s test was used to compare serum creatinine levels post-transplantation between vasculitis patients and controls.

Results

Ten patients (eight males and two females) with ANCA-associated vasculitis received 10 kidney transplants between 1987 and 2000. All patients had reached ESRF as a result of biopsy-proven focal necrotizing glomerulonephritis/pauci-immune crescentic glomerulonephritis. One patient was excluded because of the development of a positive test for anti-glomerular basement membrane antibodies that had previously been negative. Of the remaining nine patients (seven males and two females), one received a graft from a living-related donor and eight from cadaveric donors. Five patients had Wegener’s granulomatosis and four had microscopic polyangiitis. These patients had a mean age of 49.2 years (range 35–70 years) at time of transplantation. The ANCA status at diagnosis and whether ANCA were present at the time of transplantation and currently are shown in Table 1. All transplanted patients were treated with a standard immunosuppressive regime, comprising triple therapy with prednisolone, azathioprine and cyclosporin. Transplantation occurred at a mean of 44 months (range 0–130 months) after the commencement of dialysis (Table 1). The mean time of follow-up post-transplantation was 62 months (range 12–163 months). One of the nine transplants (patient G) suffered an acute rejection in the first 3 weeks and was treated by replacing cyclosporin with tacrolimus and increasing the dose of prednisolone. At the time of last visit, the creatinine level was 150 μmol/l. Two patients (Table 1) suffered a vasculitis relapse at 40 and 50 months post-transplantation, respectively, corresponding to a relapse rate of 0.04 per patient per year. Patients who relapsed had been on dialysis for a mean of 10 months prior to transplantation as compared with a mean of 54 months for the patients who did not relapse \( (P=0.22) \). In both, the relapse was classified as minor and affected the upper respiratory tract and a nasal biopsy showed fibrous scarring with multinucleate giant cells and scattered foci of small vessel arteritis. The ANCA was weakly positive by indirect immunofluorescence at the time of relapse and of a cytoplasmic pattern (cANCA). The relapses occurred in patients with the Wegener’s granulomatosis type of vasculitis and serum creatinine levels at the time of relapse were 106 and 124 μmol/l, respectively. These relapses were treated using prednisolone, cyclophosphamide and co-trimoxazole. No patients were diagnosed with AASV after transplantation.

The control group comprised 18 patients, two for each patient with vasculitis who received a transplant. The controls were those patients transplanted immediately before and after the patient with vasculitis. The mean age of control patients at transplantation was 45.3 years (range 21–63 years). Thus, our control group was younger than the patient group (45.3 vs 49.2 years). They received 17 cadaveric and one living-related allograft. Five patients suffered an episode of acute rejection at 2 weeks, 2, 3, 40 and 63 months. These were treated by increasing the dose of prednisolone. One control developed chronic rejection at 84 months of follow-up and died due to ischaemic heart disease and one control died 2 weeks after transplantation due to the development of acute pancreatitis, acute peritonitis and pseudo-obstruction.

Table 1. Clinical data of vasculitis patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at transplantation (years)</th>
<th>Sex</th>
<th>Duration of dialysis (months)</th>
<th>ANCA status at diagnosis</th>
<th>ANCA at transplantation</th>
<th>ANCA at present</th>
<th>Relapses (no. after transplantation)</th>
<th>Serum creatinine at present (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>41</td>
<td>Male</td>
<td>12</td>
<td>PR3</td>
<td>Negative</td>
<td>Positive</td>
<td>One at 40 months</td>
<td>106</td>
</tr>
<tr>
<td>B</td>
<td>44</td>
<td>Male</td>
<td>16</td>
<td>MPO</td>
<td>Negative</td>
<td>Negative</td>
<td>None</td>
<td>154</td>
</tr>
<tr>
<td>C</td>
<td>48</td>
<td>Male</td>
<td>130</td>
<td>MPO</td>
<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>132</td>
</tr>
<tr>
<td>D</td>
<td>59</td>
<td>Female</td>
<td>64</td>
<td>MPO</td>
<td>Negative</td>
<td>Negative</td>
<td>None</td>
<td>91</td>
</tr>
<tr>
<td>E</td>
<td>54</td>
<td>Female</td>
<td>68</td>
<td>MPO</td>
<td>Negative</td>
<td>Positive</td>
<td>One at 50 months</td>
<td>235</td>
</tr>
<tr>
<td>F</td>
<td>35</td>
<td>Male</td>
<td>8</td>
<td>PR3</td>
<td>Negative</td>
<td>Positive</td>
<td>None</td>
<td>150</td>
</tr>
<tr>
<td>G</td>
<td>35</td>
<td>Male</td>
<td>0</td>
<td>PR3</td>
<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>96</td>
</tr>
<tr>
<td>H</td>
<td>70</td>
<td>Male</td>
<td>84</td>
<td>PR3</td>
<td>Positive</td>
<td>Negative</td>
<td>None</td>
<td>143</td>
</tr>
</tbody>
</table>

MPO, myeloperoxidase; PR3, proteinase-3; n/a, not available.
of the colon, which was complicated by a chest infection. The level of renal function post-transplantation, as measured by serum creatinine, was better in the vasculitis cohort than in the control group and, at some time points (e.g. $P = 0.054$ at 6 months), this was significant (Table 2 and Figure 1).

**Discussion**

Despite the better recognition and improved treatment of AASV, this group of diseases continues to cause end-stage renal disease (ESRD) in a substantial proportion of patients.

Over the past 10 years, AASV has become better recognized and therapy has improved. Up to 75% of patients presenting as dialysis-dependent, recover renal function. Unfortunately, a proportion with renal involvement develops ESRF, reaching 20% in some series [4,9,10]. ESRD in AASV is usually the result of an acute rapidly progressive glomerulonephritis causing severe irreversible glomerular damage or of chronic scarring and slow progression to ESRD after a period of remission with therapy. The renal outcome of AASV patients presenting with acute renal failure is in large part determined by the rapidity with which a diagnosis is established and immunosuppressive therapy is commenced [11]. As such, the serum creatinine level at the time treatment is commenced is the single most important predictor of renal outcome. For those patients who reach ESRD, transplantation is an option, as shown by previous reports [5–7,10–15]. The outcome of these patients is of interest, particularly concerning the impact of the original disease on the transplant and vice versa. In this study we have compared patients with ESRF secondary to AASV who have received an allograft, with patients transplanted immediately before or after the patient with AASV. Thus, we have tried to account for differences in care that may occur between centres.

Renal transplantation has been recognized as an option for renal replacement therapy and reports of successful transplantation in patients with ANCA-associated Wegener’s granulomatosis, microscopic polyangitis or necrotizing crescentic glomerulonephritis date back to 1972, when Lyons and Lindsay [14] reported a successful outcome for a renal allograft in a 29-year-old man with Wegener’s granulomatosis.

The mean age of our patients at time of transplantation was 49.2 years, which is higher than in other studies. Despite their older age, the outcome of transplantation in our vasculitis patients was better at all specific times tested compared with that of the controls and this result is similar if not better than that of Nyberg’s group [15].

Our patients were older than the controls (49.2 vs 45.3 years) and this might contribute to the lower incidence of acute rejection episodes, which have been seen among elderly renal transplant recipients [16].

In our analysis, the relapse rate following transplantation in AASV was 0.04 per patient per year, which compares favourably with data from other studies [10,11], with an average time from transplantation to relapse of 45 months. This rate of relapse is lower than the expected rate reported in non-transplanted patients, which is reported as 30–45% in the literature [4,9] and is 0.07 per patient per year in our unit. The presence of ANCA at transplantation does not appear to increase the rate of relapse post-transplantation [11] and this is also true in our study, where the two patients who relapsed had a negative ANCA testing at transplantation, while the others who had a positive ANCA testing at transplantation did not relapse (Table 1). Although both our patients had cANCA, relapse is not confined to those with cANCA, but has been described in patients with pANCA also [11]. Both relapers were ANCA-positive at the time of relapse, having previously been negative, suggesting that monitoring presence of ANCA post-transplant is beneficial for high-lighting patients at risk of relapse and therefore those who may need more vigilant monitoring, in line with practice for non-transplanted individuals [12]. The mean time on dialysis prior to transplantation was 44 months (range 0–130 months), but patients who relapsed had been on dialysis for a mean of 44 months (range 0–130 months), but patients who relapsed had been on dialysis for a mean of 13 months (range 0–130 months), but patients who relapsed had been on dialysis for a mean of 13 months (range 0–130 months).
difference in the duration of dialysis before transplantation between patients who suffered a relapse and those who did not [11]. A further factor that might affect the relapse rate is the choice of post-transplant immunosuppression. The patients in this study received triple therapy with cyclosporin A, azathioprine and prednisolone. Azathioprine and prednisolone are routinely used as the maintenance immunosuppression in non-transplanted patients with AASV in our unit. Whether cyclosporin A added to a reduction in risk of relapse as previously suggested [14] remains contentious. In the previous pooled analysis of outcome in transplanted AASV patients where the overall relapse rate was 17.3%, therapy with cyclosporin A did not appear to have a significant protective effect on recurrent AASV over that afforded by other immunosuppressant regimes, including corticosteroids and azathioprine [11]. Our study would concur with this view.

In our study, vasculitis relapses affected the upper respiratory tract. By definition they were both minor. There was no renal involvement, which is interesting given that all patients lost the function of their native kidneys as a result of active vasculitis or through scarring. Other reports of recurrent AASV post-transplantation together with our study reveal a generally good response to cyclophosphamide for the treatment of relapse [11,17–19].

The recurrence of vasculitis has also been reported in non-ANCA associated autoimmune diseases, although the rates of relapse vary depending on each disease. For example, the recurrence of Goodpasture’s disease after transplantation seems to be exceedingly rare [20] and because of this we excluded one patient from our series who developed a positive test for anti-glomerular basement membrane antibody after transplantation.

In summary, renal transplantation is a beneficial option in the management of patients with AASV and ESRD. The presence of ANCA should not preclude transplantation in these patients. However, the nephrologist must be alert to the possibility of relapse to avoid a delay in commencing effective treatment.

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References


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