Brief Report

Membranous nephropathy: recurrence after kidney transplantation

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Abstract

Background. It is supposed that about 5% of dialysis patients had membranous nephropathy as a cause for their renal failure. Despite of this prevalence, only 33 cases of recurrent membranous nephropathy after kidney transplantation have been reported in the English literature.

Methods. Among 509 recipients of renal allografts, membranous glomerulonephritis was the cause of renal failure in five patients, who received six transplants.

Results. Recurrence of the disease was observed in three allografts (50%) in three patients, all of them were on treatment with cyclosporin and low-dose prednisone. Proteinuria appeared at 2, 5 and 19 months after grafting. One patient experienced a spontaneous remission after 12 months and he is free from proteinuria and with good renal function after 5 years. The remaining two patients presented progressive renal function deterioration and returned to haemodialysis 24 and 17 months after the appearance of proteinuria.

Conclusions. In this study three new cases of recurrence of membranous nephropathy are reported. One patient experienced a spontaneous remission of proteinuria. Recurrence of membranous nephropathy in renal allograft was very high in our series. Its appearance was associated with poor prognosis of the graft in most patients, although spontaneous remission of proteinuria is possible.

Key words: membranous nephropathy; renal transplantation

Introduction

Membranous nephropathy accounts for 14% of patients undergoing biopsy for glomerular disease and 30% of those patients develop end-stage-renal-disease (ESRD). According these data, Davison and Johnston [1] supposed that about 5% of dialysis patients had membranous nephropathy as a cause of their renal failure. Despite of this prevalence, only 33 cases of recurrent membranous nephropathy had been reported in the English literature, seven of them in patients on cyclosporine [2–23]. Most of these cases are single-case studies, and references to the true recurrence of the disease is variable. Recently it has been observed that cyclosporin did not prevent the recurrence of the disease [19–23]. Furthermore, the prognosis of recurrent membranous nephropathy on the graft has been considered poor and there is no effective therapy.

We report three new cases of recurrence of membranous nephropathy in cadaveric renal transplant patients on treatment with cyclosporin.

Case presentations

Between November 1979 and July 1994, 551 consecutive renal transplants were performed in our institution to 509 recipients. Glomerulonephritis, diagnosed by biopsy, was the cause of renal failure in 124 patients (24%) and membranous nephropathy in five. These five patients received six renal allografts from cadaver donors. Basal immunosuppression consisted on azathioprine and prednisone in one case and cyclosporin and low-dose prednisone in five cases. Two patients have good renal allografts function and are free from proteinuria 3 and 11 years after transplantation. These patients have not been biopsied as our criteria for biopsy is graft function deterioration (creatinine increase > 25%), or heavy proteinuria (> 2 g/24 h). Recurrence of membranous nephropathy was observed in three of four allografts performed to three patients, and its clinical course is described below.

Case 1

A 47-year-old man was admitted to our hospital because of proteinuria and oedema in July 1980. He had been in good health up to 1 month earlier when he noted ankle oedema. On admission his general condition was good and physical examination only
showed the presence of oedema in both ankles. Urinalysis uncovered a nephrotic-range proteinuria (3 g/24 h) and microhaematuria. The renal function was normal; serum urea 6.2 mmol/l (37 mg/dl) and serum creatinine (SCr) 97.2 μmol/l (1.1 mg/dl), total protein 61 g/l, and albumin 17 g/l. Complement and test for antinuclear antibody, rheumatic antigen, hepatitis B surface antigen, and ASO were normal or negative. A renal biopsy was performed. The biopsy specimen contained five glomeruli, the glomerular capillaries were patent, and the basement membranes were slightly thickened (Figure 1). Immunofluorescence showed granular deposits of IgG and C3 along all glomerular capillary walls. The patient felt well for 4 years. In 1984, renal function began to deteriorate and he started HD in July 1986. In June 1987, he received a cadaver-donor renal transplant, sharing one antigen with the donor. Basal immunosuppression consisted on CsA and low-dose prednisone. There were no episodes of rejection, and the patient was discharged on the 19th postoperative day with SCr of 106.1 μmol/l (1.2 mg/dl). In February 1989, proteinuria was detected in a routine urinalysis, reaching nephrotic range 1 month later. A transplant biopsy was performed, and light-microscopic examination showed 12 glomeruli with diffuse thickening of the glomerular capillary basement membranes. By immunofluorescence studies, diffuse and granular deposits of IgG, IgM, and C3 were found along all glomerular capillary walls. Ultrastructural studies demonstrated the presence of numerous electron-dense deposits localized on the glomerular subepithelial space (Figure 2). Renal function remained unchanged, proteinuria disappeared spontaneously in February 1990. At the present time, after 5 years, there is no protein in the urine and renal function is normal (SCr 114.2 μmol/l, 1.3 mg/dl). A new transplant biopsy has not been performed.

Case 2
A 21-year-old man presented in September 1983 with a 8-week history of oedema. The patient did not have any other complaint, and the physical examination found oedema in both ankles. The biochemical analyses were as follows; serum urea 2.5 mmol/l (15 mg/dl), SCr 88.4 μmol/l (1 mg/dl), total protein 48 g/l, and albumin 21 g/l. Urinalysis revealed proteinuria and microhaematuria. Complement and tests for antinuclear antibody, rheumatic antigen, hepatitis B surface antigen, and complement were normal or negative. On renal biopsy, glomeruli showed thickening of the mesangial matrix and subepithelial deposits. Immunofluorescence was positive for IgG in a peripheral and granular pattern. Renal function deteriorated and HD was started in January 1986. In June 1986, the patient received a cadaver-donor renal transplant, which functioned immediately. The patient shared with the donor one DR antigen. Immunosuppression consisted in CsA and low-dose prednisone. The patient was discharged on 23rd postoperative day with SCr of 132.6 μmol/l (1.5 mg/dl). In September 1986, nephrotic range proteinuria was detected. Transplant biopsy showed recurrence of membranous nephropathy. Renal function began to deteriorate and HD was restarted in October 1988. In October 1992, a second cadaver transplant was performed on the patient. The immunosuppression was CsA, azathioprine (1.5 mg/kg per day) and low-dose prednisone. Renal function was stable until June 1994, when SCr increased from 159.1 μmol/l (1.8 mg/dl) to 238.7 μmol/l (2.7 mg/dl). Transplant biopsy showed signs of chronic rejection but no recurrence of membranous nephropathy.

Case 3
A 36-year-old man, was admitted to another hospital because of nephrotic syndrome in December 1987. Renal biopsy presented changes consistent with membranous nephropathy (Figure 3). His renal function deteriorated and he was started in chronic HD in May 1991. In October 1992, he received a cadaver-donor renal transplant. No antigens were shared with the donor. The basal immunosuppression was CsA and...
Fig. 3. Case 3, patient's own kidney. Light-microscopy showing prominent basement membrane projections 'spikes' identified on the subepithelial side. (Silver-methenamine stain × 600).

low-dose prednisone. The graft functioned immediately, but on day 7, because of renal function deterioration, he was treated with four boluses of 250 mg of 6-methylprednisolone. The patient was discharged from hospital on the 13th postoperative day with a SCr of 159.1 μmol/l (1.8 mg/dl). In March 1993, he developed nephrotic range proteinuria. Graft biopsy contained six glomeruli, and presented thickening of the capillary walls with numerous subepithelial deposits. On immunofluorescence-microscopy, diffuse glomerular deposits of IgG and C3 were observed along the peripheral glomerular capillary walls (Figure 4). To control proteinuria, the dose of prednisone was increased to 1 mg/kg per day, and azathioprine (1.5 mg/kg per day) was given without success. Renal function remained unchanged until April 1994 when the patient experienced a rapid renal function deterioration, and HD was reinstituted 4 months later.

Fig. 4. Case 3, transplant kidney. Immunofluorescence study showed granular IgG deposits localized on the peripheral capillary loops (IF × 400).

Discussion

In our experience recurrence of membranous nephropathy was observed in 50% of renal allografts. No recurrence [24,25] or prevalence of recurrence between 10% and 57% have been published in the English literature. The majority of recurrences of membranous glomerulonephritis occurred in patients on azathioprine [2–18], but as described by others [19], we observed recurrence of membranous nephropathy only in patients on CsA. Only one patient with membranous nephropathy as the primary renal disease was transplanted and treated with azathioprine. Predisposing factors to the development of recurrence of the disease have not been identified. According to the available data, 77% of patients affected were male, 50% received the graft from related living donor, and 65% were below 45 years at the time of transplantation (Table 1).

Recurrence of membranous nephropathy presented between 7 days and 7 years, about 58% before the first 6 months after grafting [2–23]. In our series, recurrence of the disease took place at 19, 2 and 5 months after transplantation. Earlier recurrence was observed in the two younger patients and with rapid evolution to ESRD. The prognosis of the disease in the published cases has been as follows: graft loss with return to dialysis in several months in 40% of patients, renal function deterioration in 16% of patients, and stable renal function in the remaining 44%. Nephrotic syndrome or proteinuria persisted in all those patients with preserved renal function. The majority of patients had a follow-up under 2 years. Increasing immunosuppression in two of our patients did not influence the evolution of the nephropathy. In patient no. 3 the administration of ACE inhibitors did not change the proteinuria. These findings confirm the poor prognosis in some patients and the inefficiency of the therapies [22]. Recently, Johnston et al. [26] have reported the first successful treatment of nephrotic-range proteinuria in allograft membranous nephropathy with pulsed intravenous prednisolone followed by high-dose alternate-day oral prednisolone, but it is not clear if this patient had recurrent or de novo disease. We have observed the disappearance of nephrotic proteinuria in a patient with de novo membranous glomerulonephritis after conversion from azathioprine to CsA.

Patient no. 1 deserves special consideration. He experienced a spontaneous remission of the nephrotic syndrome and is free from proteinuria and with good renal function from five years ago. Although several patients presented a decrease of proteinuria and maintained good renal function for years, to our knowledge he is the first case of complete spontaneous remission of proteinuria. This finding suggests that spontaneous remission could be possible in recurrence of the disease in renal allograft as in primary membranous nephropathy [27,28].

Recently recurrence of membranous nephropathy
has been reported in two consecutive transplants [20,21]. In our case no. 2, we could not find any evidence of recurrence of the disease in the second transplant. That would indicate that recurrence of membranous glomerulopathy in a graft does not necessarily mean recurrence in the next transplant.

In conclusion, recurrence of membranous nephropathy in renal allograft was very high in our series. Its appearance was associated to poor prognosis of the graft in some patients, but spontaneous remission of proteinuria is possible. However, our series, as in those previously reported, is too small to draw definitive conclusions.

References

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Table 1. Clinical data of patients with recurrent membranous glomerulonephritis in renal allograft

<table>
<thead>
<tr>
<th>Author and Ref.</th>
<th>Age (years)/sex</th>
<th>To ESRD (months)</th>
<th>Donor</th>
<th>Post-transplant interval to proteinuria</th>
<th>Follow-up (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen [2]</td>
<td>23/M</td>
<td>NA</td>
<td>LRD</td>
<td>20 months</td>
<td>24</td>
<td>ESRD</td>
</tr>
<tr>
<td>Crosson [3]</td>
<td>21/M</td>
<td>53</td>
<td>CD</td>
<td>2 months</td>
<td>14</td>
<td>Proteinuria. Stable renal function</td>
</tr>
<tr>
<td>Hill [4]</td>
<td>36/F</td>
<td>60</td>
<td>CD</td>
<td>26 months</td>
<td>18</td>
<td>HD</td>
</tr>
<tr>
<td>Rubin [5]</td>
<td>21/M</td>
<td>16</td>
<td>LRD</td>
<td>2 weeks</td>
<td>14</td>
<td>SCR 4 mg/dl</td>
</tr>
<tr>
<td>Briner [7]</td>
<td>32/F</td>
<td>72</td>
<td>CD</td>
<td>24 months</td>
<td>5</td>
<td>HD</td>
</tr>
<tr>
<td>Dische [8]</td>
<td>24/M</td>
<td>36</td>
<td>CD</td>
<td>24 months</td>
<td>2</td>
<td>HD</td>
</tr>
<tr>
<td>Iskandar [9]</td>
<td>23/M</td>
<td>24</td>
<td>LRD</td>
<td>6 weeks</td>
<td>15</td>
<td>HD</td>
</tr>
<tr>
<td>Cosyns [10]</td>
<td>18/F</td>
<td>NA</td>
<td>NA</td>
<td>4 months</td>
<td>96</td>
<td>NS. Decline in renal function</td>
</tr>
<tr>
<td>First [14]</td>
<td>44/M</td>
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<td>NA</td>
<td>4 months</td>
<td>8</td>
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</tr>
<tr>
<td>Schwarz [17]</td>
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<td>NA</td>
<td>27 months</td>
<td>10</td>
<td>NS. Stable renal function</td>
</tr>
<tr>
<td>Freedman [18]</td>
<td>39/M</td>
<td>19</td>
<td>LRD</td>
<td>8 weeks</td>
<td>7</td>
<td>Increasing proteinuria</td>
</tr>
<tr>
<td>Montagino [19]</td>
<td>36/F</td>
<td>120</td>
<td>LRD</td>
<td>8 weeks</td>
<td>1</td>
<td>NS. Stable renal function</td>
</tr>
<tr>
<td>O’Meara [16]</td>
<td>36/F</td>
<td>NA</td>
<td>NA</td>
<td>30 months</td>
<td>15</td>
<td>Proteinuria. Stable renal function</td>
</tr>
<tr>
<td>Agarwal [20]</td>
<td>49/M</td>
<td>36</td>
<td>LRD</td>
<td>8 months</td>
<td>5</td>
<td>HD</td>
</tr>
<tr>
<td>Robles [21]</td>
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<td>NA</td>
<td>33 months</td>
<td>33</td>
<td>Stable renal function</td>
</tr>
<tr>
<td>Innes [22]</td>
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<td>NA</td>
<td>NA</td>
<td>2 months</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Josephson [23]</td>
<td>52/M</td>
<td>NA</td>
<td>NA</td>
<td>12 months</td>
<td>24</td>
<td>HD</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CD</td>
<td>12 months</td>
<td>34</td>
<td>HD</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CD</td>
<td>12 months</td>
<td>54</td>
<td>SCR 2.3 mg/dl</td>
</tr>
</tbody>
</table>

LRD, living related donor; CD, cadaver donor; NS, nephrotic syndrome; To ESRD: interval from diagnosis to ESRD; NA: not available
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Received for publication: 12.12.95
Accepted in revised form: 23.1.96