Long-term outcome of renal transplantation in patients with idiopathic membranous glomerulonephritis (MN)

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Abstract

**Background.** Little information is available about the long-term outcome of renal transplanted patients with idiopathic membranous nephropathy (MN).

**Methods.** The outcomes of 35 first renal transplants performed between 1975 and 2008 in patients with MN were compared with those of 70 controls transplanted in the same period and matched for sex, age and source of donors.

**Results.** The mean post-transplant follow-up was 117 ± 86 months for MN patients and 123 ± 83 months for controls. At 15 years, patient survival was 96% in patients with MN and 88% in the controls (P = ns), while graft survival rates were respectively 40% and 69% (P = 0.06). MN recurred in 12 patients (34%), namely in 4/8 (50%) patients who received the kidney from related living donors and in 8/27 (29.6%) who received the kidney from a deceased donor. Recurrence led to graft failure in six patients, all deceased donor kidney recipients, within 54 ± 33 months. The other six grafts are functioning 134 ± 73 months after transplantation. Patients with recurrence were more frequently females (42% vs 4.3%, P = 0.02). The recurrence occurred earlier (4.8 ± 3.0 vs 45.6 ± 46.9 months, P = 0.05), and there was a trend to develop a higher proteinuria (7.1 ± 5.5 vs 3.67 ± 2.6 g/24 h, P = 0.1) in grafts eventually lost because of recurrence.

**Conclusions.** The long-term patient survival was similar in renal transplant recipients with MN and in controls. The graft survival was lower in MN patients than in controls, although the difference was at borderline significance. Recurrence occurred in one-third of the patients and caused graft loss in half of them.

**Keywords:** membranous nephropathy; recurrent glomerulonephritis; renal transplantation

Introduction

Membranous nephropathy (MN) is the most frequent cause of idiopathic nephrotic syndrome (NS) in adults and may

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lead 40–50% of patients to end-stage renal disease (ESRD) in the long term [1,2]. The disease may recur after transplantation, but the impact of recurrence on the long term is still poorly defined. From the first cases of recurrence of MN on an allograft described [3,4] up to now, around 250 cases of renal transplants in patients with MN have been reported [5–15].

The Renal Allograft Disease Registry [13] and the Australian Registry [14] reported that MN was the third most frequent type of glomerulonephritis resulting in graft loss because of recurrence. The risk of recurrence was 12.5% in the Australian Registry. However, the overall incidence of graft loss at 10 years was not different in patients with MN and in those with other types of renal disease (40.1% vs 45.8%) [14].

In several single-centre series, the post-transplant recurrence rate of MN ranged between 10% and 50% [5–8,10–12,15]. This wide range of recurrence depends on the differences in the number of patients evaluated, duration of follow-up and indications to graft biopsy among the different centres. The actuarial risk of graft loss in patients with recurrent MN was estimated to be ~50% at 10 years in a previous review of the literature [10]. Probably due to the low number of patients and/or to the short-term follow-up, no definite predictors of recurrence were identified, and no treatment proved to be effective in inducing remission of recurrent MN.

The aims of this single-centre retrospective analysis were (i) to compare the long-term patient and renal allograft survival of MN patients with those of well-matched controls, (ii) to compare the long-term complications in these two groups and (iii) to evaluate the rate, the outcome and the predictors of recurrence in renal transplant recipients with MN.

Materials and methods

Patients
Of 2053 renal transplants (1721 from deceased donors and 332 from living donors) performed in our unit from July 1975 to July 2009, 35 (1.7%) were performed on adults (>18 years) with ESRD due to biopsy-proven MN. Eight of these patients received a graft from a living donor. Some of the patients included in this study have been previously described by Montagnino et al. [7].

Patients receiving a renal transplant in the same period (+3 months before or after), matched for age (+5 years), gender and source of the donor, were chosen as controls. Of 70 controls, 12 patients were carriers of autosomal dominant polycystic kidney disease, 16 had biopsy-proven glomerular diseases, 9 had a chronic non-biopsied glomerulonephritis, 2 had hypertensive nephrosclerosis, 18 had urological causes of ESRD, 2 had haemolytic uraemic syndrome, 3 had diabetic nephropathy and 8 had renal failure of unknown origin. In this last group, none of the patients had NS before the development of renal insufficiency.

Definitions

‘Recurrence’ was suspected due to the discovery of de novo proteinuria and was confirmed by renal biopsy. The presence, at renal biopsy, of capillary wall thickening at light microscopy associated with granular subepithelial immune deposits of IgG and C3 in some cases confirmed the diagnosis of recurrent membranous nephritis.

‘Biopsy policy’: Whenever an acute episode of renal dysfunction of doubtful origin or persistent proteinuria >0.5 g/day developed, the patient was submitted to graft biopsy.

‘Evaluation of renal biopsies’: All biopsies were evaluated by light microscopy and by immunofluorescence, and by electron microscopy when the specimen was available.

‘Acute rejection’ was diagnosed on the basis of a double-checked increase of 30% or more in plasma creatinine over the baseline not explained by other causes. The severity of rejection and the classification of chronic lesions were scored retrospectively according to the recently revised Banff classification [16].

‘Severe infections’: Infections requiring hospitalization.

Immunosuppression
Nine patients (26%) in the MN and 19 (27%) in the control group received prednisone and ciclosporin (CsA). Four patients (11.4%) in the MN and three in the control group (4.3%) received only CsA. Eleven MN patients (31%) and 21 (30%) controls received prednisone, CsA and azathioprine or mycophenolate mofetil (MMF). Eight MN patients (20%) and 15 controls (21.4%) received prednisone, tacrolimus and azathioprine or MMF. Three MN patients (8.5%) and eight controls (11.4%) received prednisone and azathioprine. In the control group, four patients received prednisone and sirolimus associated with CsA in three and with MMF in one.

Acute cellular rejections were treated with intravenous methylprednisolone pulses (MPP) therapy, and acute vascular rejections with antithymocyte globulins.

Statistical analysis

The statistical package S-Plus was used to analyse the sample data. Mean ± SD was used for descriptive analysis. t-test and non-parametric Wilcoxon test were used to look at the differences between the two groups of patients. Cross-tabulated data were analysed by chi-square test, or by Fisher test when the expected cell count was less than five. Survival curves were drawn using the Kaplan–Meier estimate and compared using the log-rank test. Given the non-normal distribution of the data, the impact of proteinuria on graft survival was evaluated by the calculated median value for each patient (total 3288 measures).

Results

In Table 1, the main demographic characteristics of MN patients and of controls are reported. The diagnosis of MN was made 52.8 ± 62.6 months before reaching ESRD. MN patients had been on dialysis for 51.3 ± 62.3 months before transplantation.

Patient and graft survival

The mean post-transplant follow-up was 117 ± 86 months for MN patients and 123 ± 83 for controls (P = ns).

The actuarial 15-year patient survival rates were 96% in MN patients and 88% in controls (P = 0.6) (Figure 1). Two patients in the MN group died (6%), one from sepsis and the other one from myocardial infarction after a follow-up of 34 and 216 months, respectively. In the control group, eight patients died (11.4%) after a mean follow-up of 163 ± 126 months, two from sepsis, four from cardiac failure and two from cancer. All deaths occurred with still functioning grafts. Seventeen out of 35 grafts in MN patients were lost (48%). The cause was recurrence of MN in six patients (complicated by transplant glomerulopathy in one), chronic rejection in three, unspecific sclerosing lesions in six, reduction of therapy due to Kaposi’s sarcoma in one and acute arterial graft thrombosis in the last. Twenty graft failures occurred in the control group (29%). Causes of graft failure were chronic rejection in
12 patients, unspecific sclerosing lesions in 3, primary non-functioning kidney in 1, recurrence of primary glomerular disease in 3 and acute arterial graft thrombosis in 1.

The actuarial 15-year pure graft survival rates were 40% in MN patients, and 69% in the control group (P = 0.06) (Figure 2). Excluding the six grafts lost for recurrence, renal survival of MN transplanted patients was 75% at 10 years and 53% at 15 years (data not shown).

**Post-transplant complications**

The number of delayed graft functions, of acute and chronic rejections, of unspecific sclerosing lesions, of patients with arterial hypertension, and of severe infections was not different between MN patients and controls (Table 2).

**Outcome of transplant patients with MN of the native kidney**

Among the 23 patients without recurrence, 12 never developed proteinuria during a mean follow-up of 153 ± 114.1 months after transplant. Two of these patients were biopsied because of an increase in serum creatinine 4 and 11 months after transplant; biopsy showed an acute cellular rejection in the first patient and an acute cellular rejection associated with unspecific sclerosing lesions in the second. Both patients lost the graft at 145 and 24 months after transplant. Among the other 10 patients, one died 216 months after transplant from cardiac failure, and another lost the graft 18 months after transplant due to acute arterial graft thrombosis. In the remaining eight patients, the grafts are still functioning at 179 ± 119.6 months after transplant. The other 11 patients developed non-nephrotic proteinuria at 71 ± 54 months after transplant and underwent graft biopsies that were evaluated in all cases with light microscopy and immunofluorescence and with electron microscopy in eight cases. Renal biopsy showed transplant glomerulopathy in two cases, chronic rejection in three (not evaluated with electron microscopy) and unspecific sclerosing lesions in six. Two patients still have a functioning graft at 43 and 195 months after transplant. Eight patients lost their grafts at 206 ± 44 months, and one died 34 months after transplant from sepsis.
The last 12 patients (34%) developed recurrence of MN at 26.2 ± 38.8 months after transplantation (range 1.9–126 months) which was confirmed by graft biopsy (Table 3) evaluated with electron microscopy in seven cases. The follow-up of recurrent and non-recurrent patients was not different (94.5 ± 68.3 vs 129.1 ± 92.87 months, P = ns). Six out of the 12 recurrent grafts (50%) were lost 54 ± 33 months after transplant due to recurrence in five patients and to recurrence complicated by transplant glomerulopathy in the last patient. The pure graft survival at 10 years was lower in recurrent patients (44%) than in non-recurrent patients (65%), but it was similar at 15 years (44% vs 40%) (Figure 3). Patients who lost their grafts had an earlier recurrence of MN versus those who maintained graft function (4.8 ± 3.0 vs 45.6 ± 46.9 months, P = 0.05) and also showed a higher proteinuria at the time of renal biopsy (7.1 ± 5.5 vs 3.67 ± 2.6 g/24 h, P = 0.1).

Of the eight patients with MN who received the kidney from a living donor, four had recurrence (50%) versus eight out of the 27 (29.6%) receiving their kidney from a deceased donor (P = ns). None of the four living related grafts that recurred was lost versus six out of eight deceased donor grafts (P = 0.06).

The role of proteinuria in graft function

Due to the above mentioned higher proteinuria in MN patients who lost the graft due to recurrence, the value of proteinuria as predictor of graft loss was tested in the following groups of patients:

(a) MN (1.01 ± 2.12 g/24 h) vs controls (0.36 ± 0.5 g/24 h), P = 0.044
(b) MN with (2.35 ± 3.25 g/24 h) vs those without (0.31 ± 0.42 g/24 h) recurrence, P = 0.003
(c) MN patients who lost the graft for any reason (1.75 ± 2.78 g/24 h) vs MN patients with functioning graft (0.22 ± 0.26 g/24 h), P = 0.025

(d) Controls who lost the graft (0.78 ± 1.91 g/24 h) vs controls with functioning graft (0.19 ± 0.22 g/24 h), P = 0.0016

(e) All (MN ± controls) grafts lost (1.24 ± 2.38 g/24 h) vs functioning grafts (0.19 ± 0.23 g/24 h), P = 0.005

These results confirmed the predictive values of proteinuria for graft survival.

Treatment of recurrences

In one patient, at diagnosis of recurrence continued with the basal immunosuppressive therapy, ESRD eventually developed 104 months after transplant (Table 3).
In three out of the five patients treated with angiotensin-converting enzyme (ACE) inhibitors [associated with angiotensin receptor blockers (ARB) in one], proteinuria completely remitted, while in the other two patients, proteinuria persisted with progressive deterioration of renal function.

In two other patients, ACE inhibitors were associated with three MPP, one patient achieved remission; in the second, NS persisted, and the patient eventually developed ESRD.

Two patients were treated for 6 months with MPP and prednisone alternated with cyclophosphamide [17] associated with ACE inhibitors in one. In this last patient, NS progressively remitted. The second patient achieved partial and transient remission of proteinuria, and then, NS recurred associated with a progressive worsening of graft function due to a super-imposed transplant glomerulopathy.

Two other patients treated with ACE inhibitors received rituximab (four weekly infusions in one and only one infusion in the second associated with seven plasma exchanges). The first patient achieved partial remission, and the second progressed to ESRD.

Discussion

In this study, we have reported the long-term outcome of 35 MN patients submitted to renal transplant and compared with a matched control group. The mean follow-up of our MN transplant patients was of 9.7 years, the longest reported to date to the best of our knowledge. The Australian Registry reported that the actuarial renal allograft survival at 10 years was similar in the 81 patients transplanted because of MN (40.1%) and in the 1505 transplanted patients with other types of renal disease (14). In our experience, the pure graft survival at 10 and at 15 years was lower in patients with MN than in controls; the difference was not significant, probably due to the small number of patients.

Efforts to identify clinical factors that would predict the risk for developing recurrence of MN have not been successful to date. The Renal Allograft Disease Registry reported that the post-transplant recurrence of MN was more frequent in males [13]. In none of the single-centre series was sex associated with MN recurrence [6,10,15]. Rather, we found that recurrence was significantly more frequent in females. However, these data should be seen with caution due to the small number of transplant patients with MN in this study.

It is still unclear if patients receiving a living related kidney are at higher risk of recurrence. Some old studies suggested that MN is more likely to recur in living donor grafts than in cadaveric grafts perhaps as a result of a familial predisposition to the disease [6,18]. In contrast, in the combined Lyon-Louvain Medical School series, recurrence was equally frequent in deceased and in living grafts [10], while Dabade et al. [15] observed that, among patients with recurrence, there were a numerically higher number of deceased donor kidneys. In this study, we found that recurrence occurred in half of living related patients vs 30% of deceased kidney recipients, but the number of patients was too small for any firm conclusion to be made. The time of recurrence was not different between living

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tx, transplant; ESRD, end-stage renal disease; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis.
related and deceased kidney recipients. However, although recipients of living related donors had a high rate of recurrence, the evolution of their transplant was better than that of cadaver recipients. Therefore, transplants from a living donor should not be condrainlicated in these patients.

In this series, 34% of patients developed graft recurrence of MN in a mean of 5 years after transplantation, although 8 out of 12 patients developed recurrence within the first year after transplant. Recently, [15] an even higher histological recurrence of MN (8 of 19 patients, 42%) was reported after a mean follow-up of 13 months (range 2–61 months). These 19 patients were submitted to surveillance graft biopsies at time 0, 4, 12 and 60 months after renal transplant. The initial clinical manifestations of recurrent MN were mild, with a mean proteinuria of 800 mg/day, and three patients had proteinuria within the normal range. In one patient, proteinuria never developed >1 year of follow-up. Our patients were not submitted to surveillance graft biopsies, and we cannot exclude that some of our non-recurrent patients may have developed a clinically asymptomatic histological recurrence.

The ominous prognostic value of proteinuria on graft survival is well known [19]. For this reason, we evaluated the impact of proteinuria in our study population (MN plus controls) which confirmed its relevance upon graft evolution. In our patients with recurrence of MN, those who lost their graft had higher proteinuria, although the difference was not significant, probably due to the small number of patients in our series.

However, 11 out of 23 non-recurrent patients developed proteinuria during the follow-up, and graft biopsy evaluated with light microscopy and immunofluorescence in all cases and electron microscopy in eight cases did not allow the diagnosis of recurrence of MN. We cannot exclude that some of the cases not evaluated with electron microscopy had subepithelial electron-dense deposits in addition to the other histological pictures, although none of these patients developed overt NS during a long observation. The other 12 patients never developed proteinuria during a mean follow-up of >12 years. This long observation time without proteinuria would reasonably exclude the probability of a misdiagnosed recurrence.

Six of the 12 recurrent grafts are still functioning after a mean follow-up of 11 years, while the other 6 grafts (50%) were lost because of recurrence within 5 years. Therefore, in total, 6 of 35 (17%) MN patients lost their allograft because of MN recurrence. This percentage is higher than the 6–9% reported by Briganti et al. [14] and Odorico et al. [11], but is similar to the 25% reported by Cosyns et al. [10]. Of interest, our data showed that early recurrence is an ominous prognostic sign. On the other hand, if the risk of graft failure caused by recurrence is excluded, the long-term graft survival of patients with MN was similar to that of patients with other diseases in this study as well as in other studies [9,10].

Treatment of recurrent MN is difficult. ACE inhibitors, ARB and statins are generally used to attenuate the risk of complications related to NS. In this series, most patients were treated with inhibitors of the renin–angiotensin system, and a complete remission of proteinuria was seen in three of them, although we cannot exclude that our patients entered a spontaneous remission. However, even if possible, spontaneous remission occurs very rarely in patients with post-transplant recurrence [12]. Our results are at odds with the recent report of the Mayo Clinic, in which proteinuria increased over time despite the early use of angiotensin blockade [15]. It is open to discussion whether the preemptive use of ACE inhibitors/ARB is valuable in preventing the progression of proteinuria or in treating it. A prospective study is warranted to clarify the role of ACE inhibitors/ARB. There is no convincing evidence that glucocorticoids, calcineurin inhibitors or purine synthesis inhibitors are of benefit in recurrent MN. In particular, in this study as well as in our previous report [7], calcineurin inhibitors, which are effective in native MN [20], seem not to be able to prevent the recurrence of MN in renal transplant recipients. In keeping with our data, ciclosporine or tacrolimus was not found to prevent recurrences in the experience of other authors [10,15]. Ancedotal cases of response were reported with the so-called Ponticelli regimen alternating glucocorticoids and an alkylating agent [21]. Two of our patients were treated with this regimen, and a partial remission was obtained in both; however, one of them progressed to ESRD 10 months later because of a super-imposed transplant glomerulopathy. Rituximab has been found to be successful in several cases of MN on native kidneys with non-advanced histological lesions [22,23]. Success has been reported in single cases with rituximab [24,25]. In a recent report, eight recipients with recurrent post-transplant MN and a mean proteinuria of 4.4 g/day were treated with rituximab. Twelve months post-rituximab, 75% of patients had either partial or complete remission which maintained up to the 24th month in all but one patient. Post-treatment biopsies showed resorption of electron-dense immune deposits in 6/7 cases [26]. We treated two patients with rituximab; one did not show any improvement, while the second obtained persistent partial remission.

In conclusion, although treatment of recurrent MN is still far from satisfactory, some measures seem to be helpful. In the absence of contraindications—such as renal artery stenosis, severe hyperkalaemia or severe anaemia— inhibition of the renin–angiotensin system should be offered to all patients. In cases of no response, a cyclical treatment with steroids/alkylating agents might obtain remission at least in a few patients. However, such a treatment is contraindicated in patients who have received heavy immunosuppression and should be associated with a concomitant reduction in other immunosuppressive drugs. Rituximab together with a reduction of immunosuppressive regimen may be tried early in patients with NS, before any progressive decline of renal graft function ensues. Once again, however, we recommend caution in patients heavily immunosuppressed in order to avoid severe and even life-threatening infections. Early treatment is probably more successful therefore in all patients with a history of MN, and particularly, in those receiving a kidney from a living related donor, a protocol biopsy should be performed at 3–6 months in order to recognize at an early stage recurrent lesions before the occurrence of severe proteinuria renders treatment inefficacious.
Renal transplant in membranous nephropathy

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