Spontaneous remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment

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Abstract

Background. Spontaneous remission (SR) of nephrotic syndrome, in the absence of immunosuppressive treatment, is relatively common among patients with idiopathic membranous nephropathy (IMN) and normal renal function. However, it has not been reported in patients with chronic renal impairment.

Methods. All patients with IMN who had developed SR in the presence of chronic renal insufficiency were identified among the nephrology departments that belong to the Spanish Group for the Study of Glomerular Diseases (GLOSEN). Their characteristics and outcome after SR were studied.

Results. Eleven patients were identified. All of them showed signs of renal impairment and the occurrence of SR was followed by a spontaneous decrease in proteinuria. Serum creatinine (Scr) continued to increase in the following months, reaching a peak value of 2.6 ± 1.5 mg/dL (range 1.7–6.5). Angiotensin converting enzyme inhibitors or spironolactone were prescribed in 10/11 patients at renal biopsy or shortly after it. Nephrotic proteinuria persisted during the first months of follow-up, but it started to spontaneously decrease 12 ± 7 months (2–30 months) after renal biopsy. Finally, complete (nine patients) or partial (two patients) remission of nephrotic syndrome was observed. Coinciding with proteinuria remission, renal function tended to improve. Nephrotic syndrome relapsed in two patients, accompanied by a rapid deterioration of renal function. In the remaining nine patients, remission persisted throughout a follow-up of 146 ± 64 months. Mean Scr at the last visit was 1.9 ± 0.9 mg/dL and proteinuria 0.2 g/24 h.

Conclusion. SR of nephrotic syndrome can also be observed in membranous nephropathy patients exhibiting chronic renal impairment.

Introduction

The occurrence of spontaneous remission (SR) of nephrotic syndrome, not induced by immunosuppressive therapy, is a well-known characteristic of idiopathic membranous nephropathy (IMN) [1–5]. Age at presentation <50 years old, female sex and non-nephrotic proteinuria have been considered as traditional predictors of SR. A recent study which analysed the outcome of 328 IMN patients with nephrotic syndrome, in whom an initially conservative therapeutic approach had been followed, showed that SR is relatively common among patients with massive proteinuria: 26.3% among those with baseline proteinuria 8–12 g/24 h and 21.5% among those with proteinuria higher than 12 g/24 [6]. Although this study has expanded on the clinical characteristics of IMN patients who finally develop SR, a general belief associates SR with the presence of a normal renal function. As far as we know, no studies have reported the spontaneous disappearance of nephrotic syndrome in patients with IMN and long-term, well-established chronic impairment of renal function. In the present study, we present the clinical characteristics and long-term outcome of 11 patients with biopsy-proven IMN, who presented SR in the presence of severe chronic renal insufficiency. The occurrence of SR was followed by a remarkable break in the progression of renal failure.

Materials and methods

The 14 hospitals that participated in the Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy Study, of the Grupo de Estudio de Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN) [6] were invited to collaborate in a retrospective identification of IMN patients, who had developed SR in the presence of chronic renal insufficiency. Inclusion criteria were a biopsy-proven IMN and the occurrence of an SR, either partial or complete, in the presence of chronic renal insufficiency, defined by a serum creatinine (Scr) level of >1.5 mg/dL for at least 6 months before SR. Exclusion criteria included the diagnosis of diabetes mellitus, systemic lupus erythematosus, malignancy or any other systemic disease known to be associated with secondary membranous nephropathy and immunosuppressive therapy before SR. Pertinent clinical and laboratory data were extracted from medical records at each participating centre using a uniform protocol. Estimated glomerular filtration rate (eGFR) was calculated by the Modifications in Diet and Renal Disease (MDRD) four variable equation.

A partial spontaneous remission (PR) was defined by a proteinuria value <3.5 g/24 h along with normal serum albumin in the absence of
immunosuppressive therapy. A complete spontaneous remission (CR) was defined by a proteinuria value <0.3 g/24 h in at least three consecutive visits, also in the absence of immunosuppressive therapy.

Nephrotic syndrome was defined by a proteinuria >3.5 g/day along with hypoalbuminaemia (serum albumin <3 g/dL). A relapse was defined by the reappearance of proteinuria >3.5 g/24 h, in at least three consecutive visits, in those who previously presented a partial or complete SR. Renal biopsies of the included patients were reviewed for the present study. The stage of IMN was specified in every case as well as the percentage of globally sclerosed glomeruli. Tubulointerstitial involvement (inflammatory infiltrates and fibrosis) was scored as absent, mild, moderate or severe.

**Statistical analysis**

Normally distributed variables are displayed as mean ± standard deviation. Proteinuria is expressed as median (range).

**Results**

Eleven patients who met the inclusion criteria (a biopsy-proven IMN and the occurrence of an SR, either partial or complete, in the presence of chronic renal insufficiency) were identified. They had been admitted to the participating centres during the period 1982–2000. Their demographic and clinical characteristics are summarized in Table 1. There were seven males and four females, and the mean age at the time of renal biopsy was 60 ± 10 years.

**Clinical and histological characteristics at presentation**

Nephrotic range proteinuria (6.6 g/day; 3.5–15 g/day) accompanied by hypoalbuminemia was present in all the patients. Onset of oedema ranged between 1 and 10 months before renal biopsy. All the patients showed renal insufficiency at the time of renal biopsy: Scr 2 ± 0.9 mg/dL (1.4–4.3 mg/dL) and eGFR 45 ± 21 mL/min (15–68).

Renal biopsy showed Stage 1 IMN in one patient, Stage 2 in six and Stage 3 in four. The percentage of globally sclerosed glomeruli was 19 ± 16%. Tubulointerstitial damage was scored as absent in one patient, mild in three and moderate-severe in seven. There were signs of moderate nephrosclerosis in eight patients.

The patients did not receive steroids or any other immunosuppressive therapy. Angiotensin converting enzyme (ACE) inhibitors were prescribed in seven patients at the time of renal biopsy or within the following 4 months. Spironolactone was prescribed in another two patients and one patient was treated with ACE inhibitors and spironolactone.

**Evolution after renal biopsy and occurrence of SR**

As shown in Figure 1, Scr continued to increase in all the patients after renal biopsy, in the absence of diuretic overdose or any other identifiable reversible factor. Peak Scr was 2.6 ± 1.5 mg/dL (range 1.7–6.5), reached by 21 ± 16 months after renal biopsy.

Proteinuria remained in the nephrotic range in all the patients during the first months of follow-up. However, it started to decrease 12 ± 7 months (2–30 months) after renal biopsy, in the absence of any treatment change or other identifiable causes (Figure 1). The interval between the onset of ACE inhibitors or spironolactone and the onset of proteinuria reduction was 8 ± 8 months (2–30 months). Finally, all the patients achieved PR (proteinuria <3.5 g/day) 26 ± 19 months after renal biopsy, ranging from 6 to 66 months. Proteinuria continued to decrease in 9/11 patients, achieving CR (proteinuria <0.3 g/day) 46 ± 20 months (20–78 months) after renal biopsy.

As shown in Figure 1, Scr stabilized in all the patients coinciding with proteinuria decrease and even tended to decrease after the occurrence of SR.

**Long-term follow-up, relapses and final outcome**

Mean follow-up was 142 ± 58 months (60–228). As shown in Figure 1, Scr and proteinuria remained stable during follow-up. Two patients who had achieved CR presented a relapse of nephrotic syndrome 78 and 84 months after the onset of SR. Scr values when they reached remission were 2.1 and 3.2 mg/dL, respectively. Coinciding with the recurrence of nephrotic syndrome, Scr progressively increased and both patients started chronic dialysis 12 and 23 months after the occurrence of relapse (Figure 2).

In the remaining nine patients, no relapses of the disease were detected and their clinical condition has remained stable after a mean follow-up of 146 ± 64 months. Mean Scr at the last visit was 1.9 ± 0.9 mg/dL and proteinuria 0.2 g/24 h (0–1 g/24 h).

**Table 1. Demographic and clinical characteristics**

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<th>Patient</th>
<th>Age (years)</th>
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<th>CrCl (mL/min)</th>
<th>P (g/day)</th>
<th>RAS blockade</th>
<th>Peak Scr (mg/dL)</th>
<th>Time to peak Scr (months)</th>
<th>Time to SR (months)</th>
<th>Relapse</th>
<th>Final Scr (mg/dL)</th>
<th>Final P (g/day)</th>
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aP, proteinuria; CrCl creatinine clearance.
bAt the time of renal biopsy.

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Circulating autoantibodies against PLA2R have been identified as a major antigenic target in the pathogenesis of IMN. PLA2R, a transmembrane receptor that is highly expressed in podocytes, serves as a binding site for autoantibodies in most patients with IMN [8, 9]. Nevertheless, the mechanisms implicated in the unleashing and disappearance of these autoantibodies remain unknown. A peculiarity of IMN, distinct from other primary glomerular diseases, is the high number of patients who show SR in the absence of any immunosuppressive therapy. A similar rate of SR has only been reported in children with minimal change disease in the pre-steroid era. In a recent study of GLOSEN [6], 104 of 328 patients (31.7%) with nephrotic syndrome due to IMN developed SR, with a progressive reduction of proteinuria and achieving remission 14.7 ± 11.4 months after diagnosis. SR was more frequent with lower levels of baseline proteinuria, but an important proportion of patients with massive proteinuria developed SR: 26.3% among those with baseline proteinuria >12 g/24 h and 21.5% among those with proteinuria >12 g/24 h. Baseline Scr and proteinuria, treatment with ACE inhibitors or angiotensin II type 1 receptor antagonists and a spontaneous proteinuria decrease >50% of baseline during the first year of follow-up were significant independent prediction factors for SR.

In the present study, we report on 11 patients who developed SR in the presence of chronic renal impairment. As shown in Table 1, all the patients had established chronic renal impairment at the time of renal biopsy and renal function continued to deteriorate throughout the following visits (see Figure 1). In addition, it should be considered that Scr and glomerular filtration rate calculated by means of MDRD equations underestimate the loss of renal function in nephrotic syndrome [10]. Creatinine clearance, as shown in Table 1, illustrates the severity of renal function loss in our patients. The progressive impairment in renal function was attributed to the disease’s activity since no functional disturbances such as diuretic overdosage could be identified. As usual, in IMN patients with a rapid worsening of renal function, massive proteinuria and complete nephrotic syndrome accompanied renal function deterioration. Nevertheless, proteinuria started to decrease 12 ± 7 months (2–30 months) after renal biopsy, in the absence of any treatment change or other identifiable causes. Reduction in proteinuria continued during the following months, achieving PR of nephrotic syndrome (proteinuria < 3.5 g/day) 26 ± 19 months after renal biopsy. Finally, nine patients achieved CR (proteinuria < 0.3 g/day) 46 ± 20 months after renal biopsy.

As far as we know, SR of IMN has not been reported in patients with long-term, established renal function impairment. Spontaneous disappearance of autoantibodies against PLA2R or other podocyte antigens could be a theoretical explanation for such an unexpected evolution, but specific studies monitoring these antibodies are needed to support such hypothesis.

The occurrence of even partial remission of nephrotic syndrome in IMN has a clear favourable impact on final renal outcome [11]. In our study about SR in IMN, we observed a favourable prognosis in those patients who developed SR, with a low rate (5.7%) of nephrotic syndrome relapse [6]. The rates of death and end-stage renal disease were significantly lower than in those patients whose nephrotic syndrome persisted or in those who received immunosuppressive therapies [6]. The patients reported here confirm such favourable prognosis: in spite of the advanced renal impairment that all the patients exhibited at the time of SR, renal function stabilized coinciding with proteinuria decrease and it remained stable during a long-term follow-up period (Figure 1). Only two patients, who showed a nephrotic syndrome relapse 78 and 84 months after SR, were excepted from this good outcome. As shown in Figure 2, renal function started to deteriorate coinciding with proteinuria relapse and both patients finally needed chronic dialysis treatment.

Renin-angiotensin system blockade, either with ACE inhibitors or angiotensin receptor blockers, has been associated with a greater tendency to develop SR in IMN, although this beneficial effect has only been observed in patients with proteinuria <8 g/day [5, 6]. All the patients...
included in the present report except one had been treated with ACEI inhibitors or with spironolactone, an aldosterone receptor antagonist with well-known antiproteinuric effects [12], at the time of renal biopsy or in the following months. The onset of ACE inhibitors and spironolactone preceded the onset of proteinuria reduction by 8 ± 8 months. These data could suggest some role of renin–angiotensin–aldosterone system blockade in the occurrence of SR in our patients with established chronic renal insufficiency. However, prospective randomized controlled trials are needed to demonstrate the possible beneficial effects of these drugs on the occurrence of SR in IMN.

A true estimation of the relative frequency of SR in IMN patients exhibiting chronic renal impairment is difficult because many patients who start to deteriorate renal function receive immunosuppressive treatment. A rough estimation can be derived from the data of the previous GLOSEN study about SR in IMN [6]: SR occurred in 104 patients (31.7%) and nephrotic syndrome persisted in 224 (68.2%). Among the latter, 176 patients (78.5%) initiated immunosuppressive treatment and the remaining 48 received conservative treatment. A great majority of these latter 48 patients developed chronic renal impairment without SR. The 11 patients reported here were detected by the same Nephrology Divisions participating in the previous GLOSEN study, although they were not included because of the presence of renal function impairment. Therefore, we may conclude that SR in the presence of chronic renal insufficiency appears to be uncommon in IMN, although not exceptional.

Nephrologists should be aware of the possible occurrence of SR in patients with chronic renal impairment. Our data, however, should not be interpreted as a general recommendation for conservative management in patients with IMN. In fact, we and others have reported the beneficial effect of immunosuppressive regimens in patients with severe nephrotic syndrome and deteriorating renal function in comparison with conservative treatment [4, 13]. On the other hand, the severity and chronicity of tubulointerstitial changes does not preclude response to therapy [14]. It should be understood that included patients were admitted to the participating centres during a long period of time (1982–2000) and that they were collected by a multicentre and retrospective search, not representing the application of an agreed therapeutic protocol. We think on the contrary that immunosuppression was likely indicated in most of the patients included in the study, with the obvious exception of those who refused therapy. Nevertheless, it is important to know that SR can also appear in this type of patients with a dreadful prognosis and that such SR modifies patients’ outcome.

In summary, SR can also be observed in IMN patients exhibiting chronic renal impairment, and this clinical scenario is accompanied by a clear improvement in long-term renal outcomes. More studies are needed to investigate the pathogenic mechanisms implicated in this spontaneous improvement of the disease.

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Conflict of interest statement. None declared.

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