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Spontaneous remission of nephrotic syndrome in patients with IgA nephropathy

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Abstract

Background. IgA nephropathy (IgAN) can be complicated by nephrotic syndrome. Because the spontaneous resolution of heavy proteinuria is rare, corticosteroid therapy should be considered in such cases, particularly when IgAN is combined with minimal-change disease. Here, we report our experience of spontaneous remission of nephrotic syndrome in patients with IgAN and the long-term outcomes of these patients.

Methods. Two hundred and thirty-three patients with biopsy-proven IgAN were enrolled between January 2001 and March 2009. Demographic, clinical and laboratory data were collected retrospectively based on medical records. In addition, pathologic findings were reviewed for glomerular and tubulointerstitial lesions. Outcome data for complete or partial remission, spontaneous remission, relapse, deterioration of renal function, and end-stage renal disease were recorded.

Results. Twenty-four patients (10.3%) presented nephrotic syndrome. Among them, five patients underwent spontaneous remission within 6 months after the presentation of nephrotic syndrome. Interestingly, spontaneous remission occurred even in two patients who had elevated serum creatinine levels and advanced renal damage. During follow-up, neither recurrence nor relapse occurred, and no patients showed progressive deterioration of kidney function.

Conclusions. This study suggests that spontaneous remission of nephrotic syndrome may occur in any stage of IgAN and carries a favourable long-term outcome without relapse. Given the possibility of under-reported cases, large-scale studies are required, and careful attention should be paid to such complicated cases.

Keywords: IgA nephropathy; nephrotic syndrome; spontaneous remission

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis and is an important cause of end-stage renal disease (ESRD) worldwide [1]. It is well known that IgAN slowly progresses to chronic kidney disease in all patients, and 25–30% of most published cohorts required renal replacement therapy within 20–25 years of presentation. In addition, <10% of all patients with IgAN had complete resolution of urinary abnormalities [1,2].

Even though a mild to moderate degree of proteinuria is commonly seen at different stages of IgAN, nephrotic syndrome rarely occurs. When IgAN is complicated by minimal-change disease (MCD), a trial of high-dose corticosteroids should be considered because proteinuria remits promptly in response to this therapy [3,4]. Although spontaneous remission is often reported in adult-onset MCD [5], it is uncommon in patients with nephrotic syndrome combined with IgAN. A literature review revealed that only a few cases of spontaneous resolution of heavy proteinuria in IgAN with conservative treatment have been documented [6,7]. The clinical characteristics of patients with this uncommon feature of IgAN are poorly understood due to the limited number of cases reported. Therefore, we report our experience and the long-term outcome of such patients and also provide a review of previous reports.

Materials and methods

Between January 2001 and March 2009, a total of 233 patients were diagnosed with biopsy-proven IgAN at NHIC Medical Center, Ilsan Hospital. Accordingly, all cases included in this study met the following criteria: (i) predominant mesangial deposition of IgA at least 1+ (~4+) on immunofluorescent staining, (ii) the presence of mesangial electron-dense deposits on electron microscopic studies, and (iii) the absence of other systemic inflammatory diseases such as systemic lupus erythematosus. Patients with Henoch–Schonlein purpura were excluded in this study.

Table 1. Clinical characteristics in patients with IgA nephropathy combined with nephrotic syndrome

	All	Steroid use	Non-steroid use
Number of patients	24	12	12
Age (years)	43 (9–74)	42 (9–74)	44 (19–61)
Gender (male, %)	17 (70.8%)	8 (66.7%)	9 (75.0%)
Hypertension (*n*, %)	7 (29.2%)	4 (33.3%)	3 (25.0%)
Systolic BP (mmHg)	125 (100–150)	123 (100–145)	125 (110–150)
Diastolic BP (mmHg)	78 (70–90)	78 (70–90)	79 (70–90)
Serum creatinine (mg/dL)	1.1 (0.3–2.3)	1.1 (0.3–2.3)	1.2 (0.7–2.1)
eGFR (mL/min/1.73 m^2)	71.2 (27.9–193.5)	73.4 (27.9–193.5)	67.8 (34.5–97.2)
24-h protein excretion (g/day)	6.5 (3.8–15.6)	7.0 (5.1–13.4)	5.2 (3.8–15.6)
Total cholesterol (mg/dL)	288 (241–637)	314 (242–637)	281 (241–430)
Serum albumin (g/dL)	2.7 (1.1–3.4)	2.2 (1.1–3.3)	2.9 (2.1–3.4)
Interval between presentation and biopsy (days)	6 (1–210)	4 (2–210)	7 (1–30)
Pathologic findings (Haas)			
I	5	2	3
II	2	1	1
III	6	5	1
IV	8	3	5
V	3	1	2
Clinical outcomes			
Complete remission	12	7	5
Partial remission	9	4	5
ESRD	3	1	2

All data are expressed as medians with ranges.

Among the 233 patients, 23 were lost to follow-up. Demographic and clinical data were reviewed retrospectively for age, gender, medical history, presenting symptoms, medications, time to remission and follow-up duration. We collected laboratory data including 24-h urinary protein excretion, urinary protein-to-creatinine ratio, serum creatinine, albumin and total cholesterol levels. The estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease study (MDRD) formula in adults and the Schwartz and Counahan–Barratt equation in children [8]. Pathologic findings were also reviewed for the number of glomeruli and the presence of mesangial hypercellularity, glomerulosclerosis, crescent, endocapillary proliferation, tubular atrophy, interstitial fibrosis and foot process effacement. All cases were reported based on the Haas classification system [9]. Nephrotic syndrome was diagnosed based on the presence of generalized oedema, heavy proteinuria of >3.5 g/day, hypoalbuminaemia of <3.5 g/dL, and/or hypercholesterolaemia [10]. Complete remission was defined as the absence of proteinuria (urinary protein excretion <0.3 g/day) and trace or negative urinary albumin on a dipstick test with the disappearance of oedema and normalization of biochemical findings such as hypoalbuminaemia and hypercholesterolaemia. Partial remission was defined as a reduction in proteinuria by >50% from baseline and <3.5 g/day. Recurrence was defined as the reappearance of significant proteinuria ≥1.0 g/day or >3+ urinary albumin on the dipstick test and oedema. During follow-up, complete or partial remission, spontaneous remission, recurrence, deterioration of renal function, and ESRD were recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as medians with ranges. Because the sample size was small, non-parametric tests were conducted. Variables were compared between the two groups using the Mann–Whitney *U*-test and Fisher's exact test. Significance was defined as a P-value <0.05.

Results

Characteristics of patients with IgA nephropathy presenting nephrotic syndrome

Of the 233 patients with biopsy-proven IgAN, nephrotic syndrome was present in 24 patients (10.3%) (Table 1). All 24 patients complained of generalized oedema. None of them presented gross haematuria. The median age was 43 (9–74)years, and 17 patients (70.8%) were male. Seven patients (29.2%) had hypertension, and the median serum creatinine concentration and 24-h urinary protein excretion values were 1.1 (0.3–2.3)mg/dL and 6.5 (3.8–15.6)g/day, respectively. Renin–angiotensin system (RAS) blockers such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) were prescribed in all patients except for one paediatric patient. Of the seven patients with prior hypertension, two had already been on RAS blockers, and the doses of RAS blockers were increased after the presentation of nephrotic syndrome. In the other five patients, who had been taking calcium channel blockers or beta blockers, RAS blockers were substituted or added. The median time interval between the presentation of

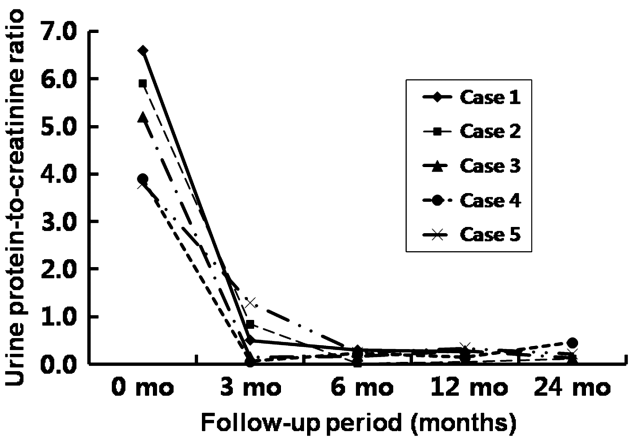

Fig. 1. The change in the urine protein/creatinine ratio during follow-up in five patients with IgA nephropathy combined with nephrotic syndrome. All patients achieved spontaneous remission within 6 months of the onset of nephrotic syndrome.

Table 2. Demographic and clinical data in patients with complete remission after steroid use and in those with spontaneous remission

Patient	Age	Gender	HTN	Presenting symptom	SBP/DBP (mmHg)	24-h U-pro (g/day)	S-Cr (mg/dL)	eGFR	SPI	S-alb (g/dL)	Time to remission (months)	FU duration (months)	S-Cr at last FU (mg/dL)	eGFR at last FU	24-h U-pro at last FU (g/day)	U-PCR at last FU	Recurrence
Complete remission after steroid use																	
1	9	M	No	Oedema	100/70	5.1	0.3	193.5	0.01	1.1	1	83	0.4	181.7	NA	0.07	Yes
2	33	M	No	Oedema	120/80	13.4	1.1	77.1	0.48	2.1	3	94	1.0	82.3	NA	0.23	Yes
3	34	M	No	Oedema	115/75	6.5	2.0	38.4	NA	1.9	6	44	1.2	68.1	0.19	0.07	No
4	43	F	No	Oedema	126/78	7.0	0.7	91.3	0.17	1.5	1	83	0.8	75.9	0.12	0.05	Yes
5	43	F	No	Oedema	110/75	6.4	1.1	54.2	0.05	2.9	9	78	1.1	52.3	NA	0.24	No
6	48	M	No	Oedema	128/80	6.3	1.8	40.5	NA	3.3	9	34	1.3	58.4	0.24	0.30	No
7	69	F	Yes	Oedema	133/85	5.0	0.6	99.1	0.21	3.0	6	24	0.7	82.5	0.17	0.12	No
Spontaneous remission in this study																	
1	34	F	No	Oedema	110/70	10.6	0.7	95.8	0.17	2.3	1	18	0.7	95.2	0.26	0.25	No
2	53	M	No	Oedema	130/80	6.6	1.3	57.8	0.23	2.9	4.5	68	1.2	62.2	NA	0.07	No
3	19	M	No	Oedema	115/75	5.2	1.2	78.0	0.15	3.0	4	47	0.9	104.6	0.12	0.15	No
4	24	M	No	Oedema	120/75	4.2	2.0	41.3	NA	2.9	6	32	1.6	52.5	0.18	0.27	No
5	38	M	No	Oedema	125/80	5.3	1.8	42.4	0.44	3.4	7	44	1.7	44.6	NA	0.28	No
Spontaneous remission in previous reports (1 and 2, Wu *et al.*; 3, Hogg *et al.*)																	
1	54	M	No	Oedema	130/80	9.5	1.0	77.9	NA	1.5	24	45	Normal	NA	Negative	NA	Yes
2	23	M	No	Oedema	120/70	6.4	0.9	104.6	NA	2.5	20	29	Normal	NA	Negative	NA	No
3	11	M	No	NA	NA	7.2	0.6	NA	NA	1.7	1.5	NA	Normal	NA	NA	NA	No

HTN, hypertension; 24-h U-pro, 24-h urine protein excretion; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); SPI, selectivity proteinuria index; S-alb, serum albumin; FU, follow-up; U-PCR, urine protein to creatinine ratio; NA, not available; M, male; F, female.

Table 3. Pathologic findings in patients with complete remission after steroid use and in those with spontaneous remission

Patient	Pathology (Haas)	No. of glomeruli	Global sclerosis (glomeruli number)	Segmental sclerosis (glomeruli number)	Mesangial hypercellularity	Endocapillary proliferation	Tubular atrophy	Interstitial fibrosis	Foot process effacement	Immunofluorescence activity
Complete remission to steroid										
1	I	28	0	0	−	−	−	−	Diffuse	IgA 1+
2	I	7	0	0	−	−	−	−	Diffuse	IgA 2+, C3 +/−
3	IV	15	4	7	>50%	+	Moderate	Moderate	Multifocal	IgA 1+, C3 1+
4	II	35	0	3	Minimal	−	−	−	Diffuse	IgA 1+, C3 1+
5	III	7	0	3	<50%	−	Mild	−	Multifocal	IgA 2+, C3 +/−
6	III	16	1	2	<50%	−	Mild	Mild	Multifocal	IgA 2+, C3 1+
7	IV	30	11	16	>50%	+	Mild	Mild	Multifocal	IgA 1+, C3 1+
Spontaneous remission										
1	I	8	0	2	−	−	−	−	Normal	IgA 2+, C3 1+
2	I	18	0	0	−	−	−	−	Diffuse	IgA 1+
3	II	6	0	2	−	−	−	−	Diffuse	IgA 2+, C3 1+/−
4	V	16	7	5	>50%	+	Mild	Mild	Diffuse	IgA 1+, C3 1+/−
5	IV	6	2	2	>50%	−	Moderate	Moderate	Multifocal	IgA 3+, C3 1+/−
Spontaneous remission in previous reports (1 and 2, Wu *et al.*; 3, Hogg *et al.*)										
1	II	26	1	0	Minimal	−	−	−	Diffuse	IgA deposit, C3 2+
2	III	9	NA	NA	<50%	−	Focal	Focal	Diffuse	IgA 4+, C3 3+
3	II	60	0	0	−	−	−	−	Diffuse	IgA 3+, C3 2+

nephrotic syndrome and the time of the renal biopsy was 6 (1–210) days. A paediatric patient who was empirically treated with corticosteroids at the first onset of nephrotic syndrome underwent a renal biopsy 210 days after the initial presentation because of frequent relapses and persistent microscopic haematuria. In all other patients, renal biopsies were performed within 1 month after presentation.

Among 24 patients, 12 (50.0%) were treated with corticosteroids. With the exclusion of the paediatric patient mentioned above, 11 of these patients received RAS blockers prior to the administration of corticosteroids. The median interval between RAS blocker treatment and corticosteroids treatment was 10 (0–88) days. In detail, 9 of these 11 patients took corticosteroids shortly after RAS blockers treatment (i.e. within 2–3 weeks), whereas corticosteroids were initiated in 2 patients 61 and 88 days after RAS blockers treatment due to persistent heavy proteinuria. The initial regimen was oral prednisolone at 1 mg/kg of body weight per day (maximum 80 mg/day) for 4–8 weeks. Prednisolone was continued at the initial dose for four more weeks when complete remission was attained, followed by subsequent tapering (e.g. dose reduction by 5–10 mg/week until reaching 5 mg/day). However, the treatment duration varied depending on the pattern of response to corticosteroids or side effects. The median duration of corticosteroids treatment was 275 (126–911) days. Among those treated with corticosteroids, complete and partial remission were achieved in seven (58.3%) and four (33.3%) patients, respectively. Recurrence occurred in three of the seven patients with complete remission, one of whom experienced recurrence during the tapering of corticosteroids. Cyclosporin was added in four patients: one with no response to corticosteroids, another with frequent relapses, and the other two patients with partial remission. Only one patient who did not respond to corticosteroids eventually progressed to ESRD.

The other 12 patients were not treated with corticosteroids because 5 underwent spontaneous remission shortly after the diagnosis, 4 did not agree to receive corticosteroids, and 3 were suffering from a gastric ulcer, pulmonary tuberculosis, and a hepatitis B infection. In the five patients with spontaneous remission, proteinuria decreased by 65–90% within 3 months after the onset of nephrotic syndrome (Figure 1). Of the remaining seven patients, five underwent partial remission, while two had persistent proteinuria and slowly progressed to ESRD.

Clinical features, pathologic findings and outcomes in patients with IgA nephropathy combined with nephrotic syndrome who underwent spontaneous remission

The five patients who underwent spontaneous remission showed similar features to those who achieved complete remission with corticosteroid treatment. When baseline parameters at the presentation of nephrotic syndrome were compared between the two groups, there were no significant differences in age, gender, 24-h urinary protein excretion, serum creatinine and pathologic findings (Tables 2 and 3). In addition, other serologic markers such as hepatitis B surface antigen positivity, C3, C4 and serum IgA levels were comparable between the two groups (data not shown). All patients showed diffuse or multifocal foot process effacement on electron microscopy, except for one patient with spontaneous remission, who presented generalized oedema and 24-h urinary protein excretion of 10.6 g, but underwent spontaneous remission before renal biopsy (Table 3, Patient 1). Interestingly, spontaneous remission occurred for all subclasses of IgAN. Three patients who underwent remission had a Haas classification of I or II, whereas the remaining two patients had a Haas classification of IV and V, respectively (Table 3). In addition, the elapsed time to remission was not different between patients with spontaneous remission and those treated with corticosteroids who achieved complete remission. In five patients with spontaneous remission, no relapse or recurrence occurred, while three patients in the corticosteroid treatment group

experienced recurrence. Renal function remained stable in both groups during the follow-up period (Table 2).

Discussion

The most common clinical feature of IgAN is asymptomatic haematuria with or without proteinuria. However, in rare instances, this can be complicated by nephrotic syndrome, and ~5% of patients with IgAN simultaneously display MCD [3,4]. Similar to those with adult-onset idiopathic MCD, many, but not all, of these patients respond well to corticosteroids [11]. Recently, we have encountered several cases of spontaneous remission of nephrotic syndrome combined with IgAN. This study provides a summary of such cases, and based on our experience, we have attempted to define the clinical characteristics of this uncommon manifestation of IgAN.

To date, five IgAN patients who presented nephrotic syndrome underwent spontaneous remission at this centre. However, because these patients were treated with ACEis or ARBs, the term 'spontaneous' may not be completely accurate. However, complete disappearance of proteinuria is very unlikely to be achieved by RAS blocker treatment alone because it has been reported that RAS blockers can decrease urinary protein excretion by 30–40% from the baseline at best, even though the extent of decrease is diverse [12,13]. In addition, the improvement in clinical and laboratory parameters such as oedema, heavy proteinuria and elevated serum cholesterol levels occurred within 6 months after presentation in these patients. Moreover, spontaneous remission occurred regardless of the subclass of IgAN. Surprisingly, heavy proteinuria disappeared spontaneously in two patients with diffuse proliferative or advanced glomerulonephritis and elevated serum creatinine concentrations. Our findings contrast with the results of previous reports [6,7] in several ways. First, all patients in our study underwent spontaneous remission within a short period of time after the onset of nephrotic syndrome, whereas complete remission was delayed for up to 2 years in the previous reports (Table 2). In fact, heavy proteinuria decreased spontaneously by >80% within 1–3 months after the presentation of nephrotic syndrome in all of the study subjects (Figure 1). Second, in previous reports, all patients displayed less severe pathologic lesions. Although the Haas classification system was not available at that time, the IgAN cases in the earlier studies can be classified as class II or III when such a classification system was applied on the basis of the pathologic findings described in the previous reports. In contrast, in our study, spontaneous remission occurred even in patients with an advanced subclass of IgAN. As suggested in the previous reports, MCD might have been present coincidentally in Patient 1–3. However, the pathologic findings in Patient 4 and 5 were not compatible with the definition of MCD. It is possible that the heavy proteinuria in these two patients could be due to other forms of nephrotic syndrome or advanced glomerular injury caused by IgAN per se. Even if this is the case, however, spontaneous disappearance of heavy proteinuria is very unusual when glomerulosclerosis and inflammation are clearly evident. Acute insult to podocytes irrespective of chronic mesangial injury may have been superimposed on top of underlying IgAN and have resolved spontaneously. However, the underlying mechanism requires further investigation.

Interestingly, patients who underwent spontaneous remission had similar features to those who achieved complete remission with corticosteroid therapy. Although detailed statistical analysis was not feasible due to the small number of cases in both groups, baseline parameters appeared to be comparable between the two groups with respect to age, gender, 24-h urinary protein excretion, serum creatinine levels and the pathologic findings (Tables 2 and 3). Furthermore, elapsed time to remission was also similar in the two groups. These findings may complicate the choice of therapeutic options in clinical practice; because clinical parameters are not distinguishable between the two groups, it is uncertain whether corticosteroid therapy should be postponed for a certain amount of time based on the expectation of spontaneous remission of nephrotic syndrome in patients with IgAN. As Hogg and Savino suggested, therapeutic trials in these patients may provide misleading conclusions if the resolution of nephrotic syndrome is falsely attributed to corticosteroid treatment rather than spontaneous remission [7]. As long as nephrotic syndrome is not promptly resolved, delaying corticosteroid therapy cannot be justified due to undesirable complications during the heavy proteinuric period, particularly when patients have severe symptoms or are at risk of complications such as renal vein thrombosis. However, spontaneous remission can be expected in patients who show a substantial decrease in heavy proteinuria without the use of corticosteroids shortly after the onset of nephrotic syndrome, as observed in our subjects.

Our study had several shortcomings. First, this study was retrospective in nature, and only a small number of patients were evaluated. Therefore, whether our findings can be generalized needs to be further investigated. In particular, our data should be interpreted with caution because advanced pathologic findings were observed in only two patients, and the small number of glomeruli in some patients may not be sufficient to evaluate the severity of glomerular injury. Second, because one patient with spontaneous remission had a short follow-up duration, the favourable prognosis of this patient may not be conclusive. However, the other patients with spontaneous remission in our study and those described in previous reports did not show deterioration of renal function without recurrence. Therefore, it is likely that these patients did indeed have a favourable outcome. Third, the chance of coincidental MCD cannot be completely excluded. Nevertheless, even though highly selective proteinuria is not consistently observed in adult MCD [14], data on the selectivity index of our subjects suggest that the incidence of coincidental MCD was unlikely to be high. Finally, 24-h urine collection was not available for constant monitoring of proteinuria during the follow-up. Urine was obtained when assessing remission after a urinary dipstick test for proteinuria became negative or trace. However, 24-h urine collection is burdensome and is therefore not routinely checked; thus, the urine protein-to-creatinine ratio is usually performed in the setting of outpatient clinics to monitor proteinuria, given the finding that random urine protein-

to-creatinine ratios can be reliably used to assess the degree of proteinuria [15].

In conclusion, our results suggest that spontaneous remission of nephrotic syndrome may occur in any subclass of IgAN, and patients with spontaneous remission may have favourable outcomes without relapse. Although a detailed analysis to identify factors associated with spontaneous remission could not be performed due to the limited number of cases, spontaneous remission of nephrotic syndrome in IgAN is noteworthy. Given the possibility of under-reported cases, large-scale studies are required, and careful attention should be paid to such complicated cases.

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Conflict of interest statement. None declared.

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Effect of furosemide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial

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Abstract

Background. In chronic kidney disease (CKD), loop diuretics correct volume-dependent hypertension, but their effect on left ventricular mass index (LVMI) is unknown.

Methods. Forty hypertensive CKD patients (estimated creatinine clearance 60–15 mL/min/1.73 m²), treated with renin–angiotensin system (RAS) inhibitors, were randomized to receive furosemide or non-diuretic antihypertensive treatment (control group). Office blood pressure (BP) <130/80 mmHg was pursued in both groups. Primary end point was the reduction of LVMI after 52 weeks. Secondary aims were to verify safety related to furosemide treatment