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Comparative study of IgA nephropathy with and without crescents

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Abstract

Glomerular crescents were analyzed as a prognostic factor in retrospectively reviewed data from 144 patients with biopsy-proven IgA nephropathy. Crescents were found in 26 (18%) patients, and detected in 2 to 100% of glomeruli in each specimen. In 5% of the patients more than 50% of the glomeruli were affected. Thirty patients with IgA nephropathy without crescents were studied as a control group. Mean age was 30.3 ± 9.4 and 30.2 ± 12.0 years for the patients with and without crescents, respectively, and males prevailed in both groups. The length of follow-up was 23.2 ± 41.6 months for patients with crescents and 29.3 ± 35.3 months for patients without crescents. Eighty percent of the patients with crescents were hypertensive, compared to 27% of the non-crescent control group ($P < 0.05$). Mean serum creatinine at the time of diagnosis was 3.9 ± 2.9 and 1.9 ± 2.1 mg/dl for the patients with and without crescents, respectively. Initial urinary protein excretion was higher in patients with crescents (4.6 ± 3.5 *vs* 1.2 ± 0.9 g/day; $P < 0.05$). At the end of follow-up 17 patients (77.3%) from the crescent group and 3 (11.1%) from the non-crescent group had end-stage renal disease ($P < 0.0001$). The presence of crescents was associated with higher levels of initial serum creatinine and urinary protein excretion, and a higher frequency of hypertension and progression to end-stage renal disease.

Key words
• IgA nephropathy
• Crescents
• Renal failure
• End-stage renal disease
• Creatinine

Introduction

IgA nephropathy is said to be the most common form of primary glomerulonephritis worldwide (1), especially in Europe and some countries in Asia and Oceania, where 20 to 47% of the kidney biopsies receive this diagnosis (2-5). In the Americas, IgA nephropathy is found in approximately 10% of the cases biopsied in Uruguay, USA and Brazil (6-8). This frequency can be higher (up to 29%) among patients with hematuria and proteinuria without nephrotic syndrome (8). In addition to genetic predisposition and environmental factors, clinical presentation at the time of the biopsy may influence the prevalence of the disease.

In 40 to 50% of patients, recurrent macroscopic hematuria is the main clinical sign of IgA nephropathy, which usually coincides with mucosal infection or exercise, notably in younger patients (9). Despite intensive

investigation by several groups, a widely accepted hypothesis for the pathogenesis of IgA nephropathy has not yet emerged. Some studies have correlated mucosal airway infection with hyperactivity of the immune system, leading to an overproduction of this IgA1 and IgA2, and elevation of serum IgA levels and kidney tissue depositon (10). Moreover, 35 to 50% of patients with IgA nephropathy have elevated serum IgA levels, especially of the IgA1 subclass, derived from bone marrow (11). IgA1 is the subclass found in renal tissue (notably in the mesangium). Whether in IgA nephropathy circulating IgA1 is bound to antigens in the form of immune complexes is still a controversial issue, in spite of the well-known recurrence of acute disease after mucosal infectious episodes. Circulating IgA from patients with IgA nephropathy exhibits abnormal glycosylation that could enhance its affinity for mesangial receptors, leading to mesangial deposition (12). Furthermore, impaired hepatic clearance of IgA1 with this glycosylation defect may also contribute to the elevation of serum levels of IgA (13).

Microscopic hematuria with or without proteinuria can be found in 30 to 50% of cases and its detection depends on urine testing. Nephrotic syndrome and renal failure are unusual (5%), although at our institution 25% of the patients with IgA nephropathy present nephrotic syndrome (14). Renal failure and hypertension are common, being detected in 59 and 53% of our patients, respectively (14).

End-stage renal disease (ESRD) can develop in 20 to 40% of patients with IgA nephropathy at 10 to 20 years of follow-up (9,15). Most studies have identified the extent of proteinuria and renal insufficiency as the most powerful predictors of a poor outcome (16). Male gender, young age at the onset of the disease, absence of recurrent macroscopic hematuria, persistent microscopic hematuria, and hypertension are also implicated as risk factors for a worse prognosis (15). Diffuse proliferative glomerulonephritis and the extent of glomerulosclerosis, interstitial fibrosis and crescents are considered to be markers of a poor prognosis (9,15). However, when multivariate analyses are performed to control serum creatinine, these markers are not considered to be independent risk factors for a worse outcome (15,17). However, comparisons among studies concerning prognosis are limited. Methodological approaches vary, and the influence of different treatment regimens cannot be assessed.

In view of the high frequency of IgA nephropathy among our patients without nephrotic syndrome, and the elevated prevalence of renal failure in patients with IgA nephropathy at our institution, the objective of the present study was to describe the frequency of crescents and the renal outcome in patients with IgA nephropathy treated at University Hospital, Faculty of Medicine, University of São Paulo.

Patients and Methods

Between January 1980 and January 2001, 144 patients with biopsy-proven IgA nephropathy were retrospectively identified in a 2000-bed tertiary care complex in São Paulo. Patients older than 14 years and without clinical evidence of systemic disease were included. All patients were followed by the Nephrology Division staff, and received only diuretics and anti-hypertensive medication as needed. Data about demographic variables, hypertension, serum creatinine, urinary protein excretion, and the presence of crescents in the renal biopsy were obtained from the medical charts. Specimens with less than 6 glomeruli were excluded from analysis. The end of follow-up was the last visit of the patient to the Nephrology Division.

Of the 144 cases with IgA nephropathy, 26 had crescents in renal tissue. We selected another 30 patients of similar age and sex

among patients without crescents for comparison of demographic data, diagnosis of hypertension, serum creatinine, and proteinuria, at the time of diagnosis. At the end of follow-up, serum creatinine and the need for dialysis were also determined for both groups.

Statistical analysis

Data were compared by the chi-square test or Fisher exact test when appropriate and mean data (± SD) were compared by the Student *t*-test, with the level of significance set at P = 0.05.

Results

Crescents were found in 18% (26/144) of the IgA nephropathy patients and were detected in 2 to 100% of the glomeruli in each specimen, although in only a small proportion of cases (5%) did they affect more than 50% of the glomeruli. Patient data are presented in Table 1. The mean age of patients with and without crescents was 30.3 ± 9.4 and 30.2 ± 12.0 years, respectively, and males predominated in both groups. The duration of follow-up was 23.2 ± 41.6 months and 29.3 ± 35.3 months for patients with and without crescents, respectively. Eighty percent (12/15) of the patients with crescents were hypertensive, in contrast to 27% (3/11) of the patients without crescents (P < 0.05). Data concerning hypertension were not available for 30 patients. Mean serum creatinine values at the time of biopsy (initial creatinine) were 3.9 ± 2.9 and 1.9 ± 2.1 mg/dl for the patients with and without crescents, respectively (P < 0.05). Initial urinary protein excretion was higher in patients with crescents (4.6 ± 3.5 g/day) than in the patients without crescents (1.2 ± 0.9 g/day), P < 0.05.

Serum creatinine values at the end of follow-up (final creatinine) were also different between groups: 8.0 ± 3.7 *vs* 2.2 ± 2.8 mg/dl for crescent and non-crescent patients (P < 0.0001). At the end of follow-up 40% of the patients had ESRD: 17 (77.3%) patients with crescents required dialysis therapy compared to 3 (11.1%) non-crescent patients (P < 0.0001). Renal survival data were not available for 4 patients with crescents and for 3 patients without crescents.

Discussion

Formerly considered to be as a benign entity, IgA nephropathy can progress to ESRD in 20 to 40% of patients, depending on the population studied (9,15). In Australia/New Zealand IgA nephropathy is as common as diabetic nephropathy as a single etiology of ESRD and is the leading cause of ESRD among Japanese patients with glomerulonephritis (5,18). In Brazil there are no available data about IgA nephropathy as a cause of ESRD.

However, a recent report by the Registry of Glomerulonephritis of the State of São Paulo (19) showed that IgA nephropathy is a common glomerular disease found in 17.7% of biopsied patients. The institutions comprising this Registry are specialized in nephrology and nephropathology. Thus, these data are not representative of the frequency of IgA nephropathy in the health care services of Brazil as a whole. Underdiagnosis of IgA nephropathy might be an important issue in our country. There is no screening policy for renal disease in Brazil and only symptomatic

Table 1. Clinical and functional characteristics of IgA nephropathy patients with crescents and without crescents.

	With crescents	Without crescents
No. of patients	26	30
Age (years)	30.3 ± 9.4	30.2 ± 12
Gender (male:female)	1.9:1.0	2.0:1.0
Time of follow-up (months)	23.2 ± 41.6	29.3 ± 35.3
Initial serum creatinine (mg/dl)	3.9 ± 2.9	1.9 ± 2.1*
Final serum creatinine (mg/dl)	8.0 ± 3.7	2.2 ± 2.8*
Proteinuria (g/24 h)	4.6 ± 3.4	1.2 ± 0.9*
Hypertension	12 (15) 80%	3 (11) 27%*

Data are reported as means ± SD. *P ≤ 0.05 compared to patient with crescents (Student *t*-test).

and/or more clinically compromised patients reach the health care services and can be identified. There are only few kidney biopsy centers and in most of them immunofluorescence microscopy, necessary for the diagnosis of IgA nephropathy (20), is not available. Therefore, the impact of IgA nephropathy on the prevalence of glomerular diseases and among ESRD patients in Brazil warrants further investigation.

In contrast to other nephrology centers (9,15), our patients with IgA nephropathy present a high frequency of renal failure and hypertension. The high occurrence of progression to ESRD among our IgA nephropathy patients probably reflects the more severe cases of IgA nephropathy referred to our service. The patients with crescents in our population had a higher prevalence of hypertension, proteinuria and renal failure, recognized as the most powerful risk factors for progression to ESRD (9,15,18). These results are similar to other reports. Hogg et al. (21) found crescents in 20% of 218 pediatric patients with IgA nephropathy. After at least 4 years of follow-up, 42% of the patients that reached ESRD had crescents in their biopsies, in contrast to 13% of dialysis-free patients. Yoshikawa et al. (22) showed that the percentage of crescents was five times higher in patients with IgA nephropathy and a glomerular filtration rate <60 ml min^{-1} (1.74 m^2)$^{-1}$.

Haas et al. (7), studying the effect of the histologic parameters of IgA nephropathy and prognosis (renal survival) by univariate analysis, showed that the presence of crescents was associated with a worse prognosis in patients with IgA nephropathy characterized by focal proliferative glomerulonephritis. In the multivariate analysis, however, when controlled for serum creatinine, the presence of crescents had no independent influence on renal survival. The only parameters independently associated with poor outcome were proteinuria >2 g/day and hypertension (7).

Treatment of IgA nephropathy has been changing in recent years. Since angiotensin II plays an important role in the pathogenesis of proteinuria, blockade of the renin-angiotensin system is the therapy of choice for patients with proteinuric nephropathy (23). Even in patients without hypertension, the use of angiotensin-converting enzyme inhibitors and AT1-receptor antagonists, alone or in combination, reduces urinary protein excretion and slows the decline in renal function (24).

The treatment of IgA nephropathy has become more aggressive regarding the use of immunosuppression. According to Pozzi et al. (25), patients with creatinine levels of 1.5 mg/dl and proteinuria between 1 and 3.5 g/24 h should be treated with methylprednisolone followed by oral prednisone for at least six months. Ballardie and Roberts (26) treated patients with loss of renal function (creatinine >1.5) with prednisone, cyclophosphamide and azathioprine, and obtained a significant reduction in the development of renal disease during the three years of follow-up. Regarding IgA nephropathy with crescents, other investigators have proposed the use of immunosuppression with prednisone, cyclophosphamide and azathioprine for at least six months (27,28). It was not possible to evaluate the impact of any treatment on our patients since this was a retrospective study regarding a period (1980-2001) during which different therapeutic approaches were used.

In conclusion, patients with crescents developed a high frequency of ESRD at the end of follow-up at our institution. The presence of crescents was associated with higher levels of initial serum creatinine and urinary protein excretion, as well as with the frequency of hypertension and progression to ESRD.

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