Original Article
A case series of diffuse crescentic IgA nephropathy: an omitted entity in the Oxford classification

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Abstract: Background: The Oxford classification of IgA nephropathy (IgAN) and subsequent validation studies failed to reveal the prognostic value of crescents. However, in these studies, crescents never involved the majority of glomeruli. In fact, diffuse crescent IgAN (DC-IgAN), with crescents involving ≥ 50% of glomeruli, is rarely reported. Methods: We analyzed 164 patients diagnosed with primary IgAN from 2000 to 2013. The patients were divided into three groups: 1) no crescent involvement, 2) crescent involvement < 50%, and 3) crescentic involvement ≥ 50% (DC-IgAN). Clinicopathological features, treatment responses, and outcomes were compared among groups. Results: Crescents were found in 25 patients (15.2%), of whom 13 (7.9%) presented with crescent involvement in ≥ 50% of total glomeruli. Compared with the other groups, DC-IgAN patients had higher serum creatinine values, proteinuria, frequency of hypertension, and lower albumin levels. Histologically, the DC-IgAN group demonstrated more globally sclerotic glomeruli and a greater degree of interstitial fibrosis/tubular atrophy, as well as more frequent extension of IgA to peripheral capillary loops on immunofluorescence examination (53.8% vs. 25% and 23.7% in the negative and < 50% crescent groups, respectively). In the DC-IgAN group, 8 patients received the same therapeutic regimen (cyclophosphamide and methylprednisolone for 6 months and azathioprine for maintenance), and only 2 patients did not have a satisfactory response to this treatment. Conclusion: The DC-IgAN variant of IgAN is associated with more severe clinicopathological features and may respond to therapy. DC-IgAN should be included in future revisions and validations of the IgAN Oxford classification to improve prognostic power and patient management.

Keywords: IgA nephropathy, Oxford classification, renal biopsy, crescents

Introduction

IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide. It is characterized by a variable clinical course ranging from a slow clinical progression with asymptomatic microscopic hematuria to rapid kidney failure [1-3]. The most common cause of rapidly progressive IgAN is diffuse crescentic IgAN (DC-IgAN) [4], defined as > 50% crescentic glomeruli on kidney biopsy. However, this condition has not been well characterized in the medical literature.

Histologically, IgAN is characterized by IgA deposition within the mesangium and sometimes also along the glomerular capillary walls, leading to mesangial cell hypercellularity, ma-

trix expansion, and occasionally crescents [5]. The reported prevalence of crescents among IgAN cases ranges from 5% to 60% [6-9]. Numerous studies have identified potential clinical, laboratory, and histological predictors for the progression of IgAN. The recent Oxford classification (developed by the International IgA Nephropathy Network) identified four morphological parameters with prognostic value; however, the presence of crescents was not associated with poor outcome because patients with rapidly progressive kidney failure were excluded from the development of this classification [10]. Subsequently, validation studies of the Oxford classification have reported conflicting results regarding the correlation between crescents and clinical outcomes [11-14]. However, these studies were heterogeneous with respect to the

degrees of crescent formation they assessed and rarely involved cases with more than 40% of glomeruli affected by crescents. In fact, cases of DC-IgAN are rare, occurring in only 1-4% of patients with IgAN, and to our knowledge there is only one study available in the literature that describes cases of this entity [15], in which the authors admitted that not all of the patients had crescents in 50% or more glomeruli.

This study was undertaken to compare the clinicopathological features of IgAN patients with different degrees of crescents ($\geq$ 50% and < 50%) and those without crescents. Immunosuppression responsiveness was also assessed. This study contributes to the limited reports available concerning this phenomenon as well as sheds light on the new studies related with similar subjects.

Materials and methods

We reviewed all kidney biopsy reports, slides, and records of 164 patients who had been diagnosed with primary IgAN between 2000 and 2012. Patient information such as epidemiological data, laboratory tests, and histological findings was recorded. Patients with known concomitant liver disease or lupus were excluded. Henoch-Schonlein purpura was excluded based on the presence of extrarenal clinical signs (that is, abdominal pain, arthritis, and purpura) found at the time of biopsy or during the follow-up. All our IgAN patients with crescentic were negative for ANA (antinuclear antibodies), antineutrophil cytoplasmic antibodies (ANCA) or serology for hepatitis B and C and HIV. Biopsies were obtained from the files of the Renal Pathology Laboratory in the Department of Pathology at the Ribeirao Preto Medical School, University of São Paulo, Brazil. The study is in accordance with the principles of the Declaration of Helsinki as revised in 2000 and were also approved by the local University Ethics Committee. Informed consent was exempted by the committee.

Histological data

Three cores of renal tissue were processed for light and electron microscopy and direct immunofluorescence, respectively, according to standard techniques. For light microscopy, the tissues were fixed in Bouin's solution embedded in paraffin, and 2- or 3-μm tissue sections were cut and stained with periodic acid Schiff (2 slides), Jones methenamine silver (3 slides), Masson trichrome (3 slides), and hematoxylin and eosin (HE) (2 slides). Each slide contained 2 to 3 sections. Glomeruli were considered to exhibit crescent formation when more than two layers of cells were observed in Bowman's space. The crescents were classified as cellular (> 50% of the lesion occupied by cells), fibrocellular (< 50% cells and < 90% matrix), or fibrous (> 90% matrix). For accurate analysis of the presence and number of crescents, only samples with 10 or more glomeruli were included in the study. In the group with crescent involvement < 50%, two cases had small glomerular sample (< 10 glomeruli). In these two cases the number of glomerular sample was increased by analysis of HE frozen section and immunofluorescence report. For immunofluorescence, fresh frozen tissue was cut into 3-μm-thick sections using a cryostat and stained with fluorescein isothiocyanate-conjugated antibodies specific for human IgG, IgM, IgA, C1q, C3, kappa, lambda, and fibrin (DAKO, Produktionsvej 42, DK-2600 Glostrup, Denmark). The immune deposits were semi-quantified from 0 to 3 + positive bright. The electron microscope specimen was embedded in blocks and kept on file in the event that sections were needed.

The patients were divided into three groups: IgAN with no crescent involvement, crescent involvement in < 50% of total glomeruli or focal crescentic IgAN (FC-IgAN), and crescent involvement in $\geq$ 50% of total glomeruli (DC-IgAN). For each biopsy, the following features were evaluated: number of globally sclerotic glomeruli (GSG); extent of interstitial fibrosis and tubular atrophy (IF/AT) semiquantitatively graded from 0 to 3 (with absent = 0, mild = 1, moderate = 2, and diffuse = 3); and number of glomeruli with crescents. The data on clinical course and treatment of patients with IgAN and crescent involvement were also recorded and analyzed.

Statistical analyses

Data are expressed as mean ± standard deviation (SD) or percentages. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Groups were compared using the Kruskal-Wallis test. Differences were significant when $P \leq 0.05$.

Table 1. Epidemiological and laboratory characteristics of patients with IgAN without crescents, with < 50% crescent involvement, and with ≥ 50% crescent involvement in total glomeruli

	Without crescents	Crescents < 50%	Crescents ≥ 50%
Number of Patients	139	12	13
Age (years)	29 ± 14.1	40 ± 14.3*	27 ± 10.8
Gender (male:female)	1.1:1.0	1.0:1.2	1.3:1.0
Initial Creatinine (mg/dL)	1.3 ± 0.02	1.4 ± 0.3	3.9 ± 1.9**
Albumin (mg/dL)	3.9 ± 0.4	3.7 ± 0.2	3.3 ± 0.2**
Proteinuria (g/24 h)	1.3 ± 0.7	1.5 ± 0.6	2.9 ± 1.6**
Hypertension (> 140/90)	51 (36.7%)	5 (41.7%)	11 (84, 6%)

*$P \geq 0.05$ compared to without crescents group. **$P \geq 0.05$ compared to other two groups.

Table 2. Histopathological characteristics of IgAN without crescents, with < 50% crescents, and with ≥ 50% crescents in total glomeruli

	Without crescents	Crescents < 50%	Crescents ≥ 50%
Number of Patients	139	12	13
No. of glomeruli	17 ± 6	17 ± 8	19 ± 9
GSG	4.0 ± 2.1	4.7 ± 2.2*	10.2 ± 4.1**
Cellular crescents	-	2.6 ± 0.9	6.7 ± 4.2**
Fibrous crescents	-	2.0 ± 0.7	8.8 ± 5.1**
IF/TA	1.41 ± 0.7	1.49 ± 0.9	1.96 ± 0.8**

*$P \geq 0.05$ compared to without crescents group. **$P \geq 0.05$ compared to other two groups. GSG: global sclerotic glomeruli; IF/TA: interstitial fibrosis/tubular atrophy.

Results

There were 164 cases consistent with IgA nephropathy, and crescents were found in 25 (15.2%) of these patients, of which 13 (7.9%) presented with DC-IgAN. Patient data for the three groups are presented in **Table 1**, and the detailed morphological data are shown in **Table 2**. At the time of biopsy, cellular and fibrous crescents, globally sclerotic glomeruli, and IF/TA were higher in the DC-IgAN group than in the other groups. The DC-IgAN group was also associated with greater frequency of hypertension, serum creatinine values, and proteinuria; and lower albumin levels. In some patients without crescent, data concerning hypertension were not available.

On immunofluorescence, the number of glomeruli available for examination in individual cases ranged from 2 to 35. The degree of mesangial IgA deposition was very similar in the three groups (2.1, 2.2, and 2.4), but extension of IgA to peripheral capillary loops was found in 53.8% of patients with DC-IgAN, 25% of those with FC-IgAN, and 23.7% of patients without crescent involvement. Concomitant fibrinogen deposition (**Figure 1**) was more frequent in the ≥ 50% and crescent < 50% crescent involvement groups (30.8% and 25%, respectively) than in the crescent-negative group (15.8%). The presence of other immunoglobulins (IgM, IgG) and complement factors (C3 and C1q) was similar across the three groups.

The mean follow-up times in the groups with and without crescents were 43 and 55 months, respectively. Twenty percent of patients without crescents and 8% of patients with crescents were lost to follow-up. The outcome of all patients with respect to estimated glomerular filtration rate (GFR) calculated by the modification of diet in renal disease (MDRD) formula is shown in **Figure 2**.

In the group with ≥ 50% crescent involvement, one patient was lost to follow-up. Of the 12 patients who completed follow-up, four already presented advanced chronic histological signs and GFR lower than 15 mL/min/1.73 m^2, thus defining end stage renal disease (ESRD) at the time of biopsy. The remaining eight patients began a pulse therapy regimen with cyclophosphamide and methylprednisolone for 6 months and azathioprine for maintenance, of which two developed a requirement for dialysis, three demonstrated improved renal function and regression of proteinuria, and in three, renal function remained impaired but stable, without need of renal replacement therapy.

The group with FC-IgAN did not differ from the group without crescents with respect to treatment, which was based on laboratory and clinical criteria. Five patients underwent a pulse therapy regimen with methylprednisolone, and seven received only antiproteinuric drugs (angiotensin converting enzyme inhibitors and
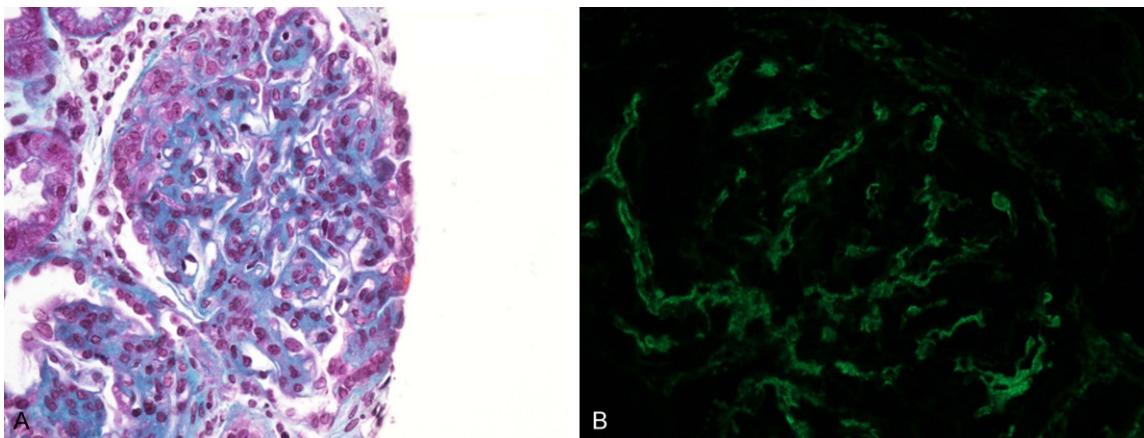
Figure 1. Histological features of DC-IgAN. A. Fibrocellular crescent together with mesangial hypercellularity (Masson's Trichrome). B. The granular deposition of fibrinogen is shown both in the mesangium and along the peripheral capillary wall.
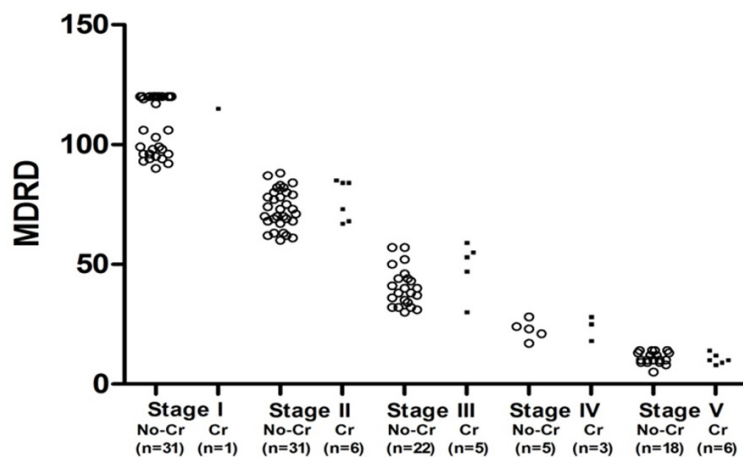

Figure 2. Distribution of 169 IgAN patients (with and without crescent) according to stage of chronic kidney disease by MDRD formula at the end of follow-up. Legends: MDRD: modification of diet in Renal Disease; Cr: groups with crescent formation; No-Cr: group without crescent formation.

significance of these crescentic lesions are unknown [7]. French and German/Greek reports and the VALIGA study (European Validation Study of the Oxford Classification of IgAN) reported that only 5%, 8.6%, and 11% of patients, respectively, had crescents [6, 13, 16], whereas recent Asian studies reported that that 60% of patients had crescents [11, 12, 17]. Hogg et al. found crescents in 20% of 218 pediatric patients with IgA nephropathy [9]. In a previous Brazilian study, the incidence of crescents in patients with IgAN was 18% [8], which is similar that observed in the present study (15.2%). A similar incidence (~18%) was also observed in the USA and several other Asian countries [7]. This difference across studies can be explained by the high geographical variability in the incidence and clinical course of IgAN, as well as biopsy practice policies.

angiotensin receptor blockers) and treatment of hypertension. On follow-up, one patient developed ERSD, six remained with stage I or II disease, and four from the pulse therapy group progressed to stage III or IV of chronic kidney disease according to the MDRD formula. One patient was also lost to follow-up.

Discussion

IgAN is the most common form of primary glomerulonephritis around the world and is characterized by a highly variable clinical course and histological picture, including crescent formation. However, the real incidence and clinical

In some cases, the disease is more aggressive, characterized clinically by progressive worsening of renal function and a great number of cellular crescent formations (≥ 50% of glomeruli). The generic term of "crescentic glomerulonephritis", or more specifically DC-IgAN, has been applied to these cases. According to a survey of

853 cases of IgAN performed by Jenette et al., the finding of 50% or more of glomeruli demonstrating crescent involvement is uncommon in IgAN, estimated to account for approximately 4% of total cases [18]. In a recent study of 430 IgAN patients, only 3 (0.7%) had crescents in ≥ 50% of glomeruli [7]. Tang et al. [15] retrospectively examined 2186 biopsies from patients with IgA disease and determined that 1.14% had DC-IgAN. Surprisingly, these results are in disagreement with our data, in which 7.9% of IgAN patients demonstrated "crescent glomerulonephritis", corresponding to approximately half the cases of IgAN with crescent formation (13 of 25 patients). Although Bantis et al. found only 3.6% of samples to contain crescents in their cohort of IgAN cases [16], similar to our findings half of those cases (53.8%) were also crescentic glomerulonephritis.

Recent studies have proposed scores for the risk stratification of IgAN. Clinical and laboratory variables associated with higher risk of loss of kidney function at presentation are proteinuria > 1 g/day, decreased GFR, and presence of hypertension [1, 2, 19]. Our patients with DC-IgAN had high levels of proteinuria and creatinine and more severe hypoalbuminemia at the time of biopsy indication compared with the other groups. Bittencourt-Dias et al. also found that patients with crescents had a higher prevalence of hypertension, proteinuria, and renal failure [8]. Among histological variables, the Oxford classification analysis concluded that mesangial hypercellularity, glomerular sclerosis, interstitial fibrosis, and atrophy were each independently associated with GFR loss. There was no conclusion about the prognostic value of the crescents, but in subsequent prognostic validation studies, crescents were rarely extensive and never involved more than 50% of the glomeruli. Because of this limitation, crescent involvement has been suggested to have poor prognostic value. Katafuchi et al. [11] demonstrated that crescent involvement was an independent predictor of renal outcomes in Japanese IgAN patients. In a study of pediatric IgA nephropathy, the presence of crescents was also predictive of poor outcome [14]. However, several other studies, including the VALIGA study, failed to demonstrate the prognostic value of crescents [7, 12, 13, 17]. However, in these studies, crescents were found in a minority of glomeruli (< 40%). Thus, a possible explanation for the absence of an impact of crescent involvement on IgAN prognosis is the fact that crescents respond to immunosuppressive therapy. After concluding that crescent lesions were not an independent prognostic factor in IgAN, Lee et al. emphasized the need for further studies including cases of IgAN with a rapidly progressive nature, since in their sample only three patients had a rapidly progressive course [7].

Any glomerulonephritis with crescent involvement in > 50% of glomeruli requires early consideration for immunosuppression. However, there is no current consensus on the treatment of IgAN with crescents. McIntyre et al. suggested that IgAN with crescent involvement can be effectively and safely treated with a low-cost regime based on oral corticosteroids and cyclophosphamide for further 2 years [20]. In another study, Rocatello et al. showed that a short course of cyclophosphamide and prednisone therapy was also effective [21]. Steroids and intravenous cyclophosphamide for 6 months have been tested [22]. In our study, eight of 12 patients in the DC-IgAN group received the same therapeutic regimen (cyclophosphamide and methylprednisolone for 6 months and azathioprine for maintenance), and only two patients did not have a satisfactory response to this treatment. The remaining four patients already presented ESRD when biopsied. Similar results have been reported by other authors who used combined cyclophosphamide/steroid treatments. However, no randomized controlled study of therapies for IgAN with crescents has been performed, and a limitation of all the above-mentioned studies is the small number of patients they included (≤ 12). Furthermore, none of these previous studies made a distinction between cases with less than 50% vs. 50% or more glomeruli showing crescent involvement. In our FC-IgAN group, the therapeutic protocol followed the traditional criteria for IgAN [23, 24]. Nevertheless, 40% of these patients (4 individuals) had poor clinical outcomes. Some authors argue that a more aggressive treatment should be considered for all patients with ≥ 10% cellular crescent involvement associated with nephrotic proteinuria and/or rapidly progressive or chronic renal failure [5, 22, 25].

Recently, another clinical entity has been reported: crescentic IgA nephropathy associated with ANCA [16]. In crescentic IgAN, ANCA-positive patients had a more severe histologi-

cal profile. But mesangial hypercellularity was markedly increased in ANCA-negative compared with ANCA-positive patients. IgA deposits along the capillary wall were detected only in ANCA-negative cases. All our patients were negative for ANCA antibodies, and about half of them demonstrated IgA extension to peripheral capillary loops. Also, all our DC-IgAN cases show some degree of endocapillary hypercellularity. Although ANCA-positive patients presented with rapidly deteriorating kidney function and more serious histological lesions, their response to aggressive immunosuppressive treatment was favorable [16, 26]. ANCA-positive patients with crescentic IgAN also are treated with a combination of cyclophosphamide and corticosteroids.

IgM deposition associated with IgA was reported to be higher in patients with IgAN and crescents compared to those with general IgAN [15]. Additionally, the presence of IgG has been associated with histological and clinical markers of unfavorable prognosis [27, 28]. In our cohort, however, the same intensity of IgM and IgG was observed across the three groups. The presence of glomerular capillary wall IgA deposits was reported to associate with greater proteinuria and histological severity [27, 29, 30], including more frequent crescent formation [27, 31]. IgA deposits along the capillary wall have been observed in 42% of crescentic, ANCA-negative IgAN patients, in contrast to their absence in all ANCA-positive patients [16]. This finding is consistent with our results, where IgA deposits in peripheral capillary loops were found in 53.8% of patients with ≥ 50% crescent involvement. Therefore, to better characterize the different prognostic factors, it is recommended that the location and intensity of immunoglobulins and complement immunostaining be routinely included in the renal biopsy report.

In conclusion, DC-IgAN is a rare pattern of IgAN characterized by higher levels of proteinuria and lower serum albumin, more frequent hypertension and renal functional impairment, and more severe global glomerulosclerosis and tubulointerstitial damage in comparison with noncrescentic IgAN or cases involving a small number of crescents. These characteristics might be associated with distinct prognostic and therapeutic implications. We propose that DC-IgAN should be considered in the revision of the IgAN Oxford classification to aid in individualized patient prognosis and management and widen the scope of the classification. In addition, future multicenter studies of this unusual glomerular disease variant are required in order to confirm the significance of our findings.

Disclosure of conflict of interest

None.

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