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Original article

Evaluation of Clinical and Pathological Characteristics of Patients with IgA Nephropathy Based on Oxford Classification System: Should Crescents be Included?

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Abstract

Introduction. None of the classification systems in immunoglobulin A (IgA) nephropathy has been widely agreed or implemented by clinicians or pathologists. In order to meet this need, "Oxford Classification System", which is highly reproducible and predictive for clinical course, was developed in 2009. In the present study, we investigated clinical and pathological characteristics of patients with IgA nephropathy based on current classification and the predictivity of crescent presence on prognosis.

Methods. The study comprised 40 patients with diagnosis of primary IgA nephropathy on renal biopsy. The biopsy findings and follow-up parameters of patients were retrospectively re-evaluated. Pathological findings were examined based on the Oxford classification system. The presence of crescent formation in the specimens was noted.

Results. The presence of crescent formation was predictive of poor prognosis regarding the glomerular filtration rate (eGFR), the level of proteinuria, and mean arterial pressure (MAP).

Conclusion: Considering the importance of crescent formation in prediction of the clinical course and need for immunosuppressive therapy, it is suggested that crescent presence can be included in this classification system.

Keywords: glomerulonephritis, IgA nephropathy, Oxford classification, crescents

Introduction

IgA nephropathy is the most prevalent glomerular disease all over the world [1-3]. Although it usually displays a benign course, 10-40% of patients progresses to end-stage renal disease within 10 to 20 years [4-6]. Therefore, exposing clinical and pathological parameters that would predetermine the course of disease is important. Studies revealed that clinical signs such as hypertension, proteinuria and low baseline glomerular filtration rate (eGFR) independently influence prognosis [7-9]. IgA nephropathy is pathologically characterized by minimal lesions to diffuse proliferative glomerulonephritis under light microscope, and IgA deposition in the glomerular mesangium by immunofluorescence [10]. Certain histopathological characteristics can predict clinical course and numerous classification systems have been developed under the light of these studies [11-13]. These classification systems did not solely intend to determine prognosis but also served for the development of a common language among pathologists and clinicians to characterize the disease [14]. Within this context, the classification systems approved until today include those developed by Lee, Haas *et al.* and by the World Health Organization for lupus nephritis [11,12]. However, these classification systems could not find an extensive and common field of usage among either nephrologists or pathologists due to weak reproducibility and weak correlation with clinical course [14]. In 2009, the clinicians who were the members of International Network for IgA Nephropathy, and pathologists together evaluated the data of 265 patients from 15 centers, and they consequently created "Oxford Classification System" that included pathological parameters with high reproducibility and demonstrated relation with clinical course. The classification system consisted of mesangial hypercellularity (M), endocapillary proliferation (E), segmental sclerosis (S) and tubular atrophy-interstitial fibrosis (T) and "M E S T" scoring system was developed according to their relation with clinical course. Although they are reproducible, parameters such as crescent formation and necrosis, of which the relation with clinical course has been definitely exposed in the previous studies, have not been included in the

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classification system as they were less prevalent in the current cohort [15].
The present study was aimed to investigate clinical and pathological characteristics of patients, as well as whether predictive character of the classification could be enhanced with the inclusion of some important parameters excluded from the classification. It was suggested that the data obtained could contribute to the literature in terms of follow-up and management of patients with IgA nephropathy.

Materials and methods

The Ethics Committee approval was obtained from Non-invasive Clinical Trials Evaluation Committee of our University under the protocol number 46-IOÇ/2010 for the study.
The study was conducted retrospectively by obtaining data from patients' records and it comprised 40 adult biopsy-proven IgA patients followed-up in our Clinic for at least six months. Renal biopsy specimens of the patients were re-evaluated by a nephro-pathologist using the "Oxford Classification System" criteria [15] and were recorded in accordance with the classification. Crescent formations and presence of necrosis in the biopsy specimens were also recorded. Presence of crescent was defined as the presence of crescent formations in more than 50% of the glomeruli.
The gender and age of the patients, date of biopsy, indications for biopsy, estimated glomerular filtration rate (eGFR) calculated according to the MDRD [16] formula, presence of macroscopic or microscopic hematuria, amount of 24-hour urinary protein excretion (g/day), systolic and diastolic blood pressures, mean arterial blood pressure (which is calculated by diastolic blood pressure + (systolic blood pressure-diastolic blood pressure)/3 formula), presence of hypertension (arterial blood pressure higher than 140/90 mmHg), whether they had been currently receiving antihypertensive or immunosuppressive drugs and, if so, the name of these drugs, and whether they had chronic renal insufficiency at admission and, if any, the degree of renal insufficiency [17] were derived from patient data obtained at admission and during biopsy and were recorded.
Based on all these data obtained, end-points such as final glomerular filtration rate, mean follow-up glomerular filtration rate, difference between the initial and final glomerular filtration rates and need for use of immunosuppressive drugs were obtained. Effects of clinical and histopathological parameters on end-points were investigated by statistical methods.

Statistical analyses

Distributions of the variables were assessed by Shapiro-Wilk normality tests and using Q-Q plots. Taking sample sizes and distribution of variables into account, Student-t, ANOVA, Mann-Whitney U and Kruskal Wallis tests were used for between group comparisons; whereas, differences between matched groups were compared using paired Samples T test and Wilcoxon test. Bonferroni test was used as a post hoc test. Relation between parametric variables was evaluated by Pearson's correlation analysis; whereas, relation between non-parametric or ordinal variables was evaluated by Spearman correlation analysis. Categorical variables were analyzed using Chi-square test and Fisher's exact test. In order to determine the relations with the end-points, linear regression analysis was used for continuous dependent variables, whereas logistic and cox regression analyses were used for categorical dependent variables. Parametric data were presented as mean ± standard deviation, whereas non-parametric data were presented as median, and categorical data were presented as percentages. Statistical analyses were done using the SPSS program for Windows (SPSS version 11.0., Chicago, IL). Statistical significance was considered as $p<0.05$.

Results

Of the 40 patients enrolled in the study, 42.5% were female and the mean age of the patients at diagnosis was 39.45±12.07 years. The mean glomerular filtration rate (eGFR) at diagnosis was 79.49±31.22 ml/min/1.73m^2. Four patients had clinical symptoms of acute kidney injury (AKI) at diagnosis. Twelve of the 40 patients had hypertension and 6 of these patients had been regularly receiving renin-angiotensin system blockers (RASB). There was no patient receiving steroid or any other immunosuppressive drug at baseline. The median value for 24-hour urinary protein excretion was 1.12 g/day, with minimum excretion rate of 0.13 g/day and maximum excretion rate of 9.9 g/day. The average value for mean arterial pressure (MAP) was 92.74± 13.85 mmHg.
Considering total duration of follow-up, median follow-up period was 40.93 months with minimum follow-up period of 6 months and maximum follow-up period of 201 months (Table 1).
Twenty-five percent of the patients had macroscopic hematuria. The most common indication for biopsy was microscopic hematuria with 60%. Clinical symptoms of nephrotic syndrome were present in 7.5% of the patients and clinical symptoms of acute renal insufficiency were present also in 7.5% of the patients. Proteinuria accompanied the macroscopic hematuria in 15% and microscopic hematuria in 47.5% of the patients. Pathological level of proteinuria was present in a total of 77.5% of the patients.

Table 1. Baseline demographic and clinical characteristics of patients

Age at diagnosis (years ± SD)	39.45±12.07	
Gender		
Male	23(57.5%)	
Female	17(42.5%)	
Body Mass Index		26.45±3.75
Follow-up duration (median month)		40.93(6-201)
Mean Arterial Pressure (mmHg)	92.74±13.85	
Baseline eGFR (ml/min/1.73m^2)	79.49±31.22	
Baseline Proteinuria (median, g/day)	1.12(0.13-9.9)	
CKD stage		
Stage 1 (eGFR>=90)	3(7.5%)	
Stage 2 (eGFR 89-60)	11(27.5%)	
Stage 3 (eGFR 59-30)	13(32.5%)	
Stage 4 (eGFR 29-15)	3(7.5%)	
AKI	4(10%)	
Hypertension	12(30%)	

Table 2. Characteristic pathological features in the study group

Mesangial Hypercellularity Score	**Frequency (%)**
M 0 (≤0.5)	9(22.5%)
M 1 (>0.5)	31(77.5%)
Endocapillary Hypercellularity	
E 0 (No)	28(70%)
E 1 (Yes)	12(30%)
Segmental Glomerulosclerosis	
S 0 (No)	13(32.5%)
S 1 (Yes)	27(67.5%)
Interstitial Fibrosis -Tubular Atrophy (IFTA)	
T0 (0-25%)	20(50%)
T1 (26-50%)	14(35%)
T2 (>50%)	6(15%)
Crescent formation	
No	30(75%)
Yes	10(25%)
Necrosis	
No	33(82.5%)
Yes	7(17.5%)

Frequency of the pathological findings in each specimen is shown in Table 2. Mesangial hypercellularity was the most prevalent finding (77.5%) followed by segmental sclerosis (67.5%), whereas crescent formation and necrosis were only present in 25% and 17.5%, respectively. Total chronicity scores were moderate and severe in 50%.

During follow-up it was observed that 35% of the patients had new-onset hypertension and the prevalence of hypertensive patients in the group reached 65%, of whom 92.5% were given a RAS blocker. The mean final eGFR was 86.51±40.95 ml/min/1.73m^2 and the mean follow-up eGFR was 82.33±36.27 ml/min/1.73m^2. The median amount of urinary protein excretion at the end of follow-up period was 0.23 g/day (minimum 0.05, maximum 4.20); the median amount of the mean urinary protein excretions during follow-up period (the mean of all protein excretion during follow-up period)

Table 3. The relationship between pathological parameters and clinical follow-up parameters

	Mean follow-up eGFR (ml/min/1.73m^2) p value		**Mean follow-up Proteinuria (g/day) p value**		**Mean follow-up MAP (mmHg) p value**		**Final eGFR (ml/min/1.73m^2) p value**	
Mesengial hypercellularity								
M0	121.39±26.14	**0.001***	0.18 (0.15-0.32)	**<0.001***	85.00±8.08	**0.001***	126.88±26.64	**0.002***
M1	70.99±30.61		0.69 (0.10-5.73)		103.53±15.07		74.79±36.87	
Endocapillary hypercellularity								
E0	96.34±33.29	**<0.001***	0.30 (0.10-3.98)	**<0.001***	96.04±17.25	**0.011***	101.19±38.60	**<0.001***
E1	49.63±16.64		1.14 (0.59-5.73)		107.11±7.75		52.26±21.41	
Segmental glomerulosclerosis								
S0	108.85±36.15	**0.002***	0.21 (0.15-5.63)	**0.007***	85.18±12.57	**<0.001***	113.12±38.69	**0.004***
S1	69.55±29.13		0.69 (0.10-5.73)		106.19±12.34		73.70±36.05	
IFTA								
T0	107.84±29.34	**<0.001***	0.24 (0.10-1.41)	**<0.001***	93.20±12.69	**0.007***	115.57±32.00	**<0.000***
T1	64.02±20.94		0.69 (0.29-1.88)		103.48±19.11		65.45±25.47	
T2	40.00±12.63		3.59 (0.59-5.73)		110.28±6.40		38.79±12.13	
Crescent								
C0	92.22±34.69	**0.002***	0.35 (0.10-5.64)	**0.002***	95.62±14.18	**0.017***	97.29±39.83	**0.004***
C1	52.66±21.38		1.15 (0.29-5.73)		110.57±15.72		54.17±24.57	
Necrosis								
N0	85.41±33.37	**0.122**	0.44 (0.10-5.73)	**0.247**	97.30±14.26	**0.169**	90.54±38.51	**0.140**
N1	67.78±48.09		0.71 (0.29-1.88)		109.05±20.10		67.53±49.78	

***p<0.05**

was 0.58 g/day (minimum 0.05, maximum 4.20). The mean arterial pressure (MAP) during follow-up was 99.36±15.79 mmHg.

When the patients were evaluated individually for pathological parameters, no significant difference was determined between the groups in terms of relation of presence and absence of parameters with age and gender, with only exception that female gender was significantly more prevalent in the patient group with necrosis versus without necrosis (85.7% vs. 33.3%; p=0.011). Although the patient group was not homogeneous for age and gender, there was no difference between the groups in terms of age and gender.

The assessment of relationship between clinical follow-up characteristics and the presence or absence of pathological parameters revealed that all adverse pathological parameters except for the presence of necrosis were significantly associated with low mean follow-up and final eGFR; high mean follow-up and final proteinuria; and also high follow-up MAP (Table 3).

Glomerular filtration rates decreased as the severity of tubular atrophy-interstitial fibrosis increased. Various degrees of clearance loss were recorded at the end of follow-up in the patients with endocapillary hypercellularity, tubular atrophy-interstitial fibrosis, and crescent formation. The lowest baseline glomerular filtration rate was found in the patients with severe tubular atrophy and interstitial fibrosis; this also applied to follow-up and final glomerular filtration rates (Figure 1).

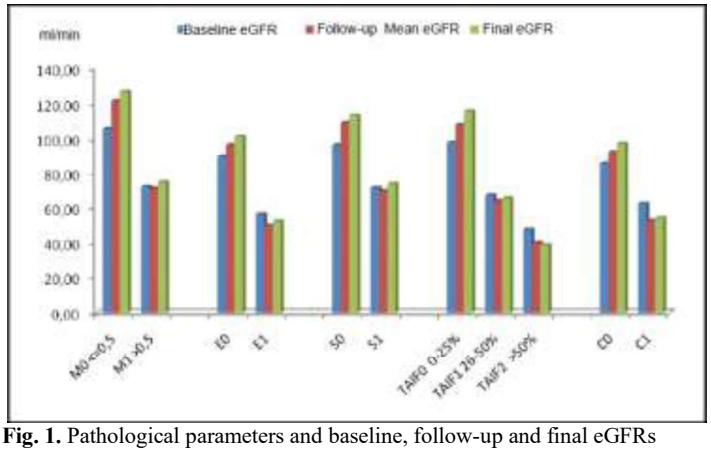

Fig. 1. Pathological parameters and baseline, follow-up and final eGFRs

With regard to all groups, decrease in the amount of follow-up and final proteinuria was conspicuous. The amounts of baseline, follow-up and final proteinuria were higher in the patients with severe tubular atrophy-interstitial fibrosis as compared to all other groups. The lowest amounts of baseline, follow-up and final proteinuria were recorded in the group without mesangial hypercellularity. Presence of all pathological parameters was associated with increased amount of proteinuria. Presence of endocapillary hypercellularity, tubular atrophy-interstitial fibrosis and crescent was associated with higher amount of proteinuria than the presence of other features (Figure 2).

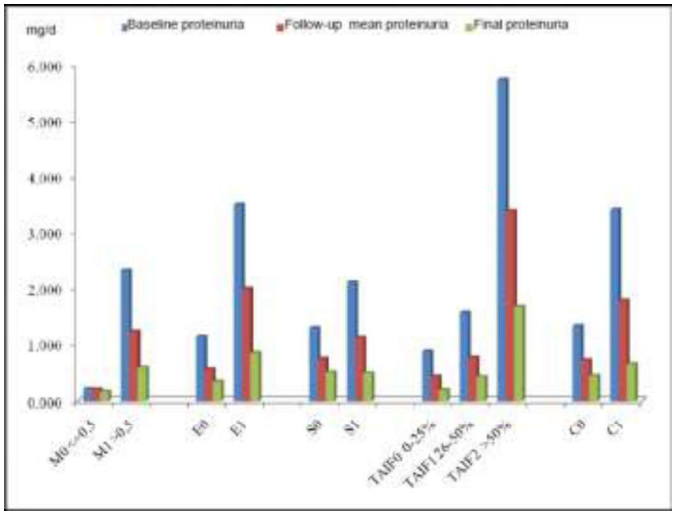

Fig. 2. Pathological parameters and baseline, follow-up and final proteinuria

Evaluation of pathological parameters by univariate regression analysis in terms of final eGFR and follow-up eGFR, which were the end-points, revealed that presence of each pathological parameter is individually a significant predictor. Evaluation of pathological parameters by univariate regression analysis for the difference in glomerular filtration rate, which was the end-point, revealed that only the presence of tubular atrophy-interstitial fibrosis and crescent formation were significant predictors (Table 4).

Table 4. Predictivity of Presence of Pathological Parameters in Clinical Course (Univariate Analysis)

	Final eGFR (ml/min/1.73m^2)		Mean follow-up eGFR (ml/min/1.73m^2)		GFR Difference (ml/min/1.73m^2)	
	β (s.d)	p	β (s.d)	p	β (s.d)	p
Mesangial Hypercellularity	-52.09(13.24)	**<0.001***	-50.40(11.26)	**<0.001***	-18.47(9.29)	0.054
Endocapillary Hypercellularity	-48.93(11.91)	**<0.001***	-46.71(10.16)	**<0.001***	-15.71(8.52)	0.073
Segmental Glomerulosclerosis	-39.43(12.46)	**0.003***	-39.30(10.64)	**0.001***	-14.56(8.38)	0.090
IFTA	-41.11(6.09)	**<0.001***	-36.22(5.43)	**<0.001***	-14.75(5.08)	**0.006***
Crescent	-43.13(13.43)	**0.003***	-39.56(11.78)	**0.002***	-20.41(8.81)	**0.026***

***p<0.05**

Discussion

In the present study, the "Oxford Classification System", which was developed by the member clinicians and pathologists of the network for IgA nephropathy and is the newest and most promising system, was investigated in our patient group in terms of reproducibility and validity for IgA nephropathy, which has yet no internationally accepted and high reproducible classification system in terms of clinical and pathological parameters although it is the leading cause of glomerulonephritis. In addition, crescent formations and necrosis, which have not been included in the system, were also evaluated and relation of pathological parameters with both clinical end-points and drug usage was explored [15,18].

Analyses clearly exposed the validity and reproducibility of the classification system and, in addition, demonstrated the relation of crescent formation, which has yet not found a place in the classification system, with poor clinical course.

In the present study, all patients that had at least 6-month follow-up data were included in the analyses without establishing any exclusion criteria in order to investigate the classification system, which is thought to be applied in all patients with IgA nephropathy, in all aspects. In this respect, it can be said that the present study is fictionally superior to the reference study of the classification system, which started with many exclusion criteria and therefore was designed in the way to exclude a group rich in acute and rapid crescent formations.

Evaluating the demographic data obtained at the end of the study, it was observed that the mean age at diagnosis was 39.75 years and there was a weak male predominance. Relatively advanced mean age determined in the present study for the patients with Ig A nephropathy, which is known to involve usually the ages of 20-to-30 years, was attributed to the absence of routine screening programs in Turkey and biopsy being saved for patients with concomitant proteinuria or loss of clearance. Literature review revealed no large-scale study that reflects the characteristics of Turkish population in terms of demographic data such as prevalence and gender distribution of IgA nephropathy, which showed significant racial difference.

The most common reason for biopsy was long-lasting and persistent microscopic hematuria accompanied or not by proteinuria (60%). Although literature suggests that macroscopic hematuria is the leading presenting symptom, this did not apply to our study group. Only 25% of the patients had macroscopic hematuria accompanied or not by proteinuria. In our patient group, the prevalence rates of baseline pathological proteinuria (77.5%) and baseline low clearance (75%) were substantially high.

The most common pathological parameter was the presence of mesangial hypercellularity (77.5%). This finding was similar with the patient population that formed the basis for the recent classification system [15]. Presence of crescent, which could have not found a place in the classification system, was observed in 25% of biopsy samples, whereas necrosis was observed in 17.5%. This rate was much lower in the patient group that formed the basis for the development of the classification system. This difference between the present patient group and the patient group that formed the basis for the classification system can be explained by exclusion of the patients with less than 1-year follow-up period and accordingly exclusion of the patients with more severe course or acute onset.

Low baseline glomerular filtration rate, high amount of baseline urinary protein excretion, and high baseline mean arterial pressure were individually associated with poor outcomes. This also applied to the data adjusted for age and gender. These findings display strong similarity with large-scale studies in the literature conduc-

ted on the clinical course of IgA nephropathy. D'Amico *et al*. published a review in 2004, which evaluated large-scale prognosis studies, and they similarly determined that high baseline proteinuria, low baseline glomerular filtration rate and high baseline blood pressure were associated with poor renal prognosis [1,2,15,19].

With regard to the contribution of pathological parameters to the clinical end-points and their predictive values, all pathological parameters excluding necrosis were found to be associated with poor end-points in univariate analyses. This was independent of age and gender of patients. This finding clearly supports the validity of the classification system. In the literature, it is clearly stated that presence of each pathological variable negatively influences the prognosis. The fact that presence of these parameters, individually or together, unfavorably influences the prognosis has also been shown by the Oxford Classification System. Endocapillary hypercellularity, the effect of which to the clinical end-points in the classification system could have not been demonstrated clearly, was among the parameters determined to unfavorably influence the clinical course, as demonstrated by Haas M. *et al*. [13] and D'Amico *et al*. [1].

Tubular atrophy-interstitial fibrosis and crescent have been underlined as independent predictors of end-points. There are many studies supporting crescent formations to be poor prognostic factors [20-23]. In the present study, definite findings about poor clinical course are an important step in revealing that classification system should be re-evaluated in terms of crescent formations.

Conclusion

The present study is one of the pioneer studies that explore the reproducibility and validity of the Oxford Classification System in adult patient group. The importance of crescent formation in predicting clinical end-points has been determined. The limitations of the study are: firstly, the study included a limited cohort of patients (40 subjects with IgA nephropathy) with a short follow-up in some patients; secondly, the number of patients with crescents represented too small subset of patients to allow clear conclusion statistically; thirdly, the lack of relation with types of crescents and clinical outcomes, and finally the relationship between the serum IgA/C3 ratio and severity of histological lesions needs to be addressed.

The results of the present study suggest that crescent formation can be included in the classification system when supported by large scale prospective studies.

Conflict of interest statement. None declared.

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