

Predictors of glomerular IgA immunostaining patterns and disease progression in IgA nephropathy patients; a 13-year study of clinical and morphological features of renal biopsies

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ABSTRACT

Introduction: IgA nephropathy (IgAN) is a common primary glomerulonephritis with highly heterogeneous clinical and histopathological features. The MEST-C scoring system has been developed to improve prognostic assessment but lacks elements related to immunostaining study.

Objectives: This study aimed to investigate the association between the immunofluorescence (IF) deposits' patterns of IgA (mesangiocapillary versus pure mesangial) with demographic, clinical, biochemical, and morphological parameters of MEST-C classification in IgAN patients.

Patients and Methods: This retrospective, cross-sectional study was conducted on 268 biopsy-proven cases of IgAN from July 2009 to July 2022 at a single laboratory in Isfahan in Iran. The demographic, clinical, and laboratory data including age, gender, serum creatinine, and proteinuria were collected from the biopsy request forms. The morphological parameters of MEST-C classification and IF study patterns were collected from the biopsy reports.

Results: The average age of all patients was 37.7 ± 13.47 years, with 67% being males. The mean serum creatinine and proteinuria levels were 1.43 mg/dL and 1730.94 mg/day, respectively. MEST-C score analysis revealed that 171 patients (63.8%) had mesangial expansion (M1), while 105 patients (39.2%) exhibited endocapillary hypercellularity (E1). Additionally, segmental glomerulosclerosis (S1) and tubular atrophy/interstitial fibrosis (T1 and T2) was observed in 160 biopsy samples (59.7%). Moreover, crescent (C) formation was noted in 76 (28.4%) of biopsies. Data analysis using univariate logistic regression demonstrated that E, T, and C on morphology, complement C3, IgG, IgM deposits on IF, and the total MEST score were all associated with an increased risk for mesangiocapillary deposits of IgA. However, using the multivariate method, the results indicated that only the total MEST score (OR: 2.4), presence of crescent (OR: 3.22), presence of endocapillary hypercellularity (OR: 4.86), tubular atrophy/interstitial fibrosis grade II (OR: 34.4), and IgG deposition (OR: 3.37) were independent risk factors for mesangiocapillary deposits of IgA.

Conclusion: The total MEST score is significantly higher in mesangiocapillary patterns. Furthermore, the presence of E1, T2, and C1-2 morphological parameters of the updated Oxford classification in renal biopsies are independent risk factors for IgA mesangiocapillary deposits. Hyperactivation of immunoglobulins and the complement system appears to contribute to mesangial-capillary proliferation.

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Introduction

IgA nephropathy (IgAN), also known as Berger's disease, is the most common form of primary glomerulonephritis worldwide (1). It is characterized by the abnormal deposition of immunoglobulin A (IgA) antibodies in the glomeruli (1). However, the exact cause of IgAN is not fully understood (2). It is believed that the immune system plays a crucial role, leading to the production of abnormal IgA antibodies. Antibodies accumulate in the glomeruli, leading to inflammation and damage over time. Common symptoms include hematuria, proteinuria, and occasionally, high blood pressure (2). Its heterogeneity, with highly variable clinical and histopathological features, makes predicting the prognosis of IgAN challenging (2). The severity and progression of IgAN can vary widely, ranging from mild with slow progression in 5–15% of patients five years after diagnosis to as high as 10–50% of patients over 20 years of diagnosis (3).

The MEST-C scoring system is an update on the original morphology-based Oxford classification for IgAN (3). The following classification is used worldwide to describe various pathological findings of kidney biopsies and to prognosticate the clinical course of patients:

- Mesangial hypercellularity (M0/M1); mesangial cell increase in the glomeruli, with M0 ($\leq 50\%$ glomeruli) and M1 ($> 50\%$ glomeruli) (3, 4).
- Endocapillary hypercellularity (E0/E1); hypercellularity in capillary loops, with E0 (absent) and E1 (present) (3,4).
- Segmental glomerulosclerosis (S0/S1); segmental sclerosis affecting part of a glomerulus, with S0 (absent) and S1 (present) (3,4).
- Tubular atrophy/interstitial fibrosis (T0/T1/T2); tubular atrophy and extent of scarring in the interstitial area, with T0 (0-25% cortical area), T1 (26-50%), and T2 ($>50\%$) (3,4).

The MEST-C scoring system incorporates crescents to the original MEST characteristics (4). Crescents refer to the presence of, cellular/fibrocellular proliferation within Bowman's space (3,4).

The combined total MEST score is 5 points (M1 + E1 + S1 + T2) (5). For updated MEST-C classification it sums upto 7 points. Renal lesions with a sum score of two or higher were considered as an independent risk factor for progression to end-stage renal disease (ESRD) in IgAN patients (5).

Immunostaining investigations reveal IgA deposits distributed in different areas of the renal parenchyma, providing valuable insights into IgAN's severity and prognosis. Typically, the deposits of IgA are located in the mesangial compartment of the glomeruli (Figure 1A). The recognition of capillary wall IgA deposition as a significant finding (Figure 1B) has improved our understanding of disease progression and prognosis (5,6). Studies have shown that the presence of IgA deposits

Implication for health policy/practice/research/medical education:

The Oxford classification of IgAN, when integrated with other morphological parameters and immunostaining patterns at diagnosis, aids pathologists and clinicians in predicting and grading the severity of IgAN in patients.

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along the capillary walls is associated with more severe kidney damage, an increased risk of renal failure, and poorer long-term outcomes (6). Approximately one-third of IgAN cases exhibit IgA deposits along the capillary walls, underscoring its importance in clinical contexts(6). The lack of some essential components within the morphology-based Oxford classification, such as the immunostaining patterns of IgA deposits and other parameters of vasculopathy, might jeopardize accurate risk stratification and treatment decisions.

Objectives

This study investigated the association between patterns of immunofluorescence (IF) deposits (mesangiocapillary versus pure mesangial) and demographic, clinical, laboratory, and morphological parameters of MEST-C in a large sample of IgAN patients.

Patients and Methods

Study design

In this retrospective, longitudinal study to establish the association of IF staining patterns with demographic, clinical, laboratory and morphological parameters, IF study formed the core component of the study. Careful scrutiny was conducted to confirm the presence of

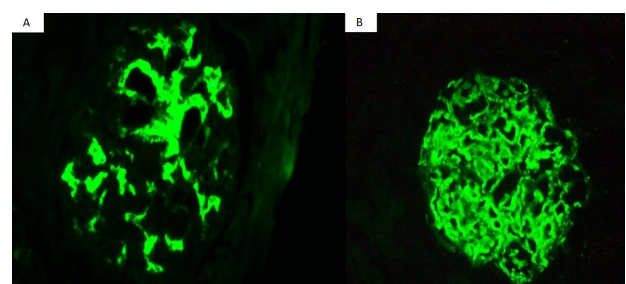


Figure 1. Immunostaining patterns of IgA deposits in IgA nephropathy (IgAN). (A) Pure mesangial deposits of IgA with 3+ intensity on a scale of 0 to 3+ in a typical case of IgAN (IF for IgA, $\times 200$). (B) Both mesangial and capillary wall deposits of IgA with 3+ intensity on a scale of 0 to 3+ in another case of IgAN (IF for IgA, $\times 200$).

immune deposits predominantly composed of IgA within the mesangial or mesangiocapillary areas using the technique of IF microscopy. The immune deposits were quantified on a scale of 0 to 3+ based on their brightness. To diagnose IgAN, it is essential to observe the existence of widespread and extensive IgA deposits graded as $\geq 2+$, along with the absence of C1q deposition (7).

Data collection

From July 2009 to July 2022, all kidney biopsies were received by our kidney pathology laboratory. Patients undergoing the biopsy had not received any prior treatment, and biopsies containing less than eight glomeruli were excluded from the study. Furthermore, patients were evaluated through a questionnaire completed upon admission for the biopsy, along with laboratory data from patients' records and a brief medical history provided by referring physicians, to confirm the absence of previous IgAN diagnosis, collagen vascular diseases, and liver cirrhosis.

After diagnosing IgAN by IF, a systematic examination of the histopathology glass slides was conducted to assess the morphological variables. These variables were then conducted in accordance with the revised Oxford classification method (3,8).

Additionally, the medical records of patients were examined to collect demographic, clinical, and laboratory data at the time of the biopsy. The data elements included age, gender, serum creatinine, and 24-hour proteinuria.

Kidney histopathology

The kidney biopsies were processed for both light and direct IF microscopies. The tissue specimens were fixed in a 10% formalin for histological sectioning. To prepare each kidney biopsy, paraffin blocks were cut into 3 μm sections, and then stained for periodic acid Schiff, hematoxylin and eosin, Jones methenamine silver, and Masson trichrome. For IF study, the sample was rapidly frozen in liquid nitrogen. The sections, which were 6 μm thick, were stained for IF analysis using fluorescein isothiocyanate (FITC)-conjugated antibodies that targeted human IgA, IgG, IgM, C1q, and C3. The IF slides were evaluated and reported by a nephropathologist using a grading scale ranging from 0 to 3+ to indicate the intensity of positive fluorescence brightness (7). The evaluation of the IF slides was conducted blindly. The pattern of IgA deposits was classified as either pure mesangial or mesangiocapillary in each case (Figure 1). This pattern was then correlated with other morphological and immunostaining parameters of IgAN.

Statistical analysis

To analyze the data, we used statistical software Statistical Package for the Social Sciences (SPSS), version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such

as mean and standard deviations (SD), were computed to summarize the data. Quantitative variables were reported as mean \pm SD or median (interquartile range) depending on distribution of data. Qualitative variables were reported as frequencies (percentages). The Levene's test was conducted to assess the equality of variances since the Kolmogorov-Smirnov test was conducted to test the normality of the data. The data variables in the two groups of patients with mesangiocapillary and pure mesangial deposits were compared using Fisher's exact test, chi-square test, Mann-Whitney U, and independent t-tests as appropriate. Univariate and multivariate logistic regression analyses were employed to explore the risk factors for immunostaining patterns of IgA deposits.

Results

This study included 268 participants with an average age of 37.7 ± 13.47 years, of whom 180 (67%) were male. The average serum creatinine level was 1.43 mg/dL, and the mean level of proteinuria was 1730.94 mg/d. Analysis of MEST-C parameters revealed that 171 (63.8%) patients exhibited mesangial hypercellularity (M1), while 105 (39.2%) displayed endocapillary hypercellularity (E1). Additionally, 160 (59.7%) patients demonstrated segmental glomerulosclerosis (S1), and a similar proportion exhibited tubular atrophy/interstitial fibrosis (T1 and 2). The crescent formation was noted in 76 (28.4%) of biopsies. The patterns of IgA deposits on IF, predominantly exhibited pure mesangial staining 212 (79.1%), since mesangiocapillary deposits were observed in 56 (20.9%) of biopsies. The average MEST total score was 2.44, out of 5 (Table 1).

Table 2 presents data on the correlation between the immunostaining deposit pattern (pure mesangial versus mesangiocapillary) and various demographic, clinical, laboratory, and morphological variables in the MEST-C classification. The total MEST score, reported as 2.02 ± 1.25 in cases of pure mesangial and 4.04 ± 0.66 in mesangiocapillary lesions, which is significantly higher in the mesangiocapillary group. However, other factors such as age, gender, serum creatinine, daily proteinuria, and the M and S parameters did not show a statistically significant relationship with the frequency of mesangiocapillary immune deposits.

Crude data analysis using univariate logistic regression was conducted to assess the risk factors predictive of the mesangiocapillary immunostaining pattern. Factors including the total MEST score, E, T, C, C3, IgG, and IgM variables were identified as predictors of mesangiocapillary deposits. Upon adjusting for confounding factors using the multivariate method, the results indicated that only the total MEST score (OR: 2.4), presence of crescent (OR: 3.22), presence of endocapillary hypercellularity (OR: 4.86), presence of tubular atrophy/interstitial fibrosis grade II (OR: 34.4), and IgG deposits (OR: 3.37) were

Table 1. Baseline characteristics of included patients and their biopsies

Variable	Sub-variable	Frequency (N)	Percent	
Gender	Male	180	67.2	
	Female	88	32.8	
MEST parameters				
M	M ₀	97	36.2	
	M ₁	171	63.8	
E	E ₀	163	60.8	
	E ₁	105	39.2	
S	S ₀	108	40.3	
	S ₁	160	59.7	
T	T ₀	108	40.3	
	T ₁	105	39.2	
	T ₂	55	20.5	
Immunoglobulin and complement				
C3	No	60	22.4	
	Yes	208	77.6	
IgG	No	183	68.3	
	Yes	85	31.7	
IgM	No	183	68.3	
	Yes	85	31.7	
Crescent	No	192	71.6	
	Yes	76	28.4	
Immunostaining pattern deposits	Pure mesangial	212	79.1	
	Mesangiocapillary	56	20.9	
Variable	Mean	SD	Min	Max
Age (year)	37.7	13.47	15	85
Total MEST score	2.44	1.41	0	5
Serum creatinine (mg/dL)	1.43	1.03	0.5	13
Proteinuria (mg/d)	1730.94	1039.58	50	7230

SD, Standard deviation; Min, Minimum; Max, Maximum.

independent risk factors for mesangiocapillary deposits (Table 3).

Discussion

IgAN is one of the most prevalent forms of primary glomerulonephritis and is noteworthy for its heterogeneity (1). It ranks as a leading cause of ESRD (1,3). Our investigation focused on determining the relationship of the IF deposit patterns with various demographic, clinical, laboratory, and morphological parameters in IgAN patients. The complexity of morphological parameters and IF patterns contributes to the challenge of accurately predicting the prognosis of IgAN in individual patients.

Prior studies have emphasized the significance of IgA deposits extending from the mesangial area into the peripheral capillary walls, along with other adverse risk factors (1). Previously Berger and Hinglais made pioneering contributions to the field by identifying diffuse mesangial staining for IgA as a critical marker for the diagnosis of this entity (1,9).

In the study by Bellur et al containing 175 IgAN biopsies, capillary wall IgA staining was observed in 15% of cases (6). They concluded that the location of glomerular IgA and the presence of IgG correlate with mesangial (M1) and endocapillary hypercellularity (E1) (6). Their findings validated our findings regarding the role of IgG and IgA in the capillary wall in the development of proliferative changes in IgAN. (6). In our study of 268 biopsies, 20.9% of patients exhibited mesangiocapillary staining of IgA, which was significantly associated with E1, T2, C, and IgG deposits.

Our previous pilot study on 114 biopsy samples of IgAN patients in 2013 also showed, among four morphological variables of the Oxford classification, only endocapillary hypercellularity exhibited a statistically significant association with mesangiocapillary deposits ($P=0.04$) (10). This finding was also validated in our current study. It should be remembered that over the past 10 years, our renal biopsies have increased to 268 cases for this extended assessment of IgAN.

Table 2. Relationship of demographic clinical, laboratory, and MEST-C characteristics with deposits

Variable	Sub-variable	Immunostaining pattern deposits				P value	
		Pure mesangial		Capillary mesangial			
		No.	%	No.	%		
Gender	Female (N = 88)	67	76.1	21	23.9	0.403*	
	Male (N = 180)	145	80.6	35	19.4		
MEST parameters	M	M ₀ (N = 97)	80	82.5	17	17.5	0.307*
		M ₁ (N= 171)	132	77.2	39	22.8	
	E	E ₀ (N= 163)	154	94.5	9	5.5	<0.001*
		E ₁ (N= 105)	58	55.2	47	44.8	
	S	S ₀ (N= 108)	91	84.3	17	15.7	0.088*
		S ₁ (N= 160)	121	75.6	39	24.4	
	T	T ₀ (N= 108)	106	98.1	2	1.9	<0.001*
		T ₁ (N= 105)	89	84.8	16	15.2	
		T ₂ (N= 55)	17	30.9	38	69.1	
	Crescent	C ₀ (N= 192)	171	89.1	21	10.9	<0.001*
C ₁₋₂ (NN= 76)		41	53.9	35	46.1		
Immunoglobulin and complement	C3	No (N= 60)	56	93.3	4	6.7	0.002*
		Yes (N= 208)	156	75	52	25	
	IgG	No (N= 175)	154	88	21	12	<0.001*
		Yes (N= 93)	58	62.4	35	37.6	
	IgM	No (N= 183)	153	83.6	30	16.4	0.008*
		Yes (N= 85)	59	69.4	26	30.6	
Variable		Mean	SD	Mean	SD	P value	
Age (y)		37.82	13.54	37.71	13.3	0.958***	
Total MEST score		2.02	1.25	4.04	0.66	<0.001***	
Serum creatinine (mg/dL)		1.43	1.11	1.46	0.66	0.122****	
Proteinuria (mg/d)		1753.09	1076.13	1647.46	892.29	0.500***	

SD, Standard deviation.

*Chi-Square; **Fisher's exact test; ***Independent t test; ****Mann-Whitney U.

The previous retrospective analysis of 545 biopsy-proven IgAN cases by Hwang et al, who validated a risk assessment model for Korean patients, highlighted the importance of M1, T1, and T2 variables in predicting kidney failure (11). Similar findings by Rui et al in 101 IgAN patients reinforced the significance of M1 and T2 in predicting poor kidney outcomes, aligning with our study's observations regarding the pivotal role of tubular atrophy/interstitial fibrosis grade II (12).

Haaskjold et al on 306 IgAN patients, demonstrated the possibility of classifying patients into risk categories based on MEST-C scores (13). Univariate analysis of M, E, S, T, and C variables revealed that all types were linked to an increased risk of ESRD (13). However, a multivariate analysis indicated that S, T, and C variables were associated with worse outcomes (13). This finding supports our study's results, emphasizing, the role of T2 and C variables as risk factors, in IgAN patients.

Another noteworthy finding from our study highlights the role of crescent lesions, with an odds ratio of 3.22,

as an independent predictor of the mesangiocapillary immunostaining pattern. The analysis by Neves et al on 111 IgAN biopsies confirmed that Oxford classification lesions of S1, T1/T2, and C1/C2 were independent risk factors for a poor prognosis (14). This variable was found to be correlated with hematuria, hypertension, elevated serum creatinine levels, and other pathological changes in various studies (14,15). These results provide support for the inclusion of crescent in the MEST criteria for predicting outcomes.

Recently, Miyabe et al examined 871 IgAN biopsies using the Oxford classification's total score (total MEST-C score). They found an association between the total score of the Oxford classification and renal prognosis. Our study also revealed that a higher total MEST score, with an odds ratio of 2.4, correlates with greater morphological injury (16).

Likewise, the study by Peng et al on the location of IgG deposits in IgAN patients identified the presence of IgG deposits in the mesangiocapillary location as

Table 3. Predictive factors for mesangiocapillary immunostaining deposits using univariate and multivariate logistic regression analysis

Variable		Unadjusted				Adjusted			
		OR	P value	95% CI		OR	P value	95% CI	
				Lower	Upper			Lower	Upper
E	E ₀	13.18	<0.001	6.39	30.8	4.86	0.018	1.31	18.05
	E ₁								
	T ₀								
T	T ₁	9.52	0.003	2.137	42.56	3.77	0.149	0.62	22.92
	T ₂	118.4	<0.001	26.13	536.9	34.4	<0.001	4.25	279.81
Crescent	C ₀	6.95	<0.001	3.66	13.17	3.22	0.028	1.13	9.15
	C ₁₋₂								
	No								
C3	No	4.66	0.004	1.61	13.49	1.08	0.922	0.20	5.85
	Yes								
	No								
IgG	No	4.42	<0.001	2.38	8.22	3.37	0.025	1.16	9.71
	Yes								
	No								
IgM	No	2.42	0.009	1.22	4.11	1.17	0.761	0.42	3.21
	Yes								
	Yes								
Total MEST score		6.81	<0.001	4.01	11.5	2.40	0.013	1.20	4.79

OR, Odds ratio; CI, Confidence interval; Ref, Reference.

an independent risk factor for a poor prognosis (17). Moreover, patients with a higher intensity of glomerular IgG deposits or C3 deposits were also associated with a lower survival rate (17). Hyperactivation of IgG, IgM, and complement C3 may play a role in extra-capillary proliferation, particularly in the context of diffuse crescent formation. Nevertheless, it is important to acknowledge that studies exploring the association between IgA immunostaining patterns, morphological parameters, and demographic data remain limited and biased. Therefore, further long-term prospective studies are required to reveal the exact pathophysiological mechanisms and immunostaining predicting factors in patients with IgAN.

Conclusion

The location of IgA deposits in the glomeruli and the presence of IgG and C3 on IF correlate with greater morphological injury. The total MEST score is significantly higher in mesangiocapillary cases than in pure mesangial lesions. Additionally, presence of E, T2, and C morphological features in renal biopsies are independent risk factors for mesangial-capillary deposits. The hyperactivation of immunoglobulins and the complement system seems to contribute to mesangial-capillary proliferation by inducing a cascade of inflammatory responses. However, no correlation was found between immunostaining patterns and the demographic, clinical, or laboratory parameters of IgAN cases in this study. Validation of these findings is required in further large-scale, multicenter, prospective, and longitudinal studies with follow-up data.

Limitations to the study

There are certain limitations to this study. It is a single

center-based, retrospective study with no data on further follow-up or treatment. Moreover, electron microscopy was not performed for the exact localization of immune deposits.

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Availability of data and materials

All pathology data consisting glass slides, blocs and pathology reports are available with the corresponding author.

Conflicts of interest

The authors have declared no competing interests. This study was conducted at Dr. Baradaran's Laboratory in Isfahan, where all biopsies were performed and prepared (<https://drbaradaranlab.com/>). Hamid Nasri, a retired Professor of Nephrology at Isfahan University of Medical Sciences, is currently collaborating as a researcher with the Department of Natural Sciences at the University of Georgia in Tbilisi, Georgia.

Ethical issues

The research was conducted under the tenets of the Declaration of Helsinki. Patients were informed about the intervention and its related complications and provided informed consent at the time of kidney biopsy. This study is longitudinal, which was started from July 2009 and now continuing. The first publication of our results was conducted in 2013 (18). In the meantime, various features of IgAN was studied. As mentioned above a preliminary data on immunostaining pattern was published in 2013 on 114 of our biopsy samples (10). Additionally, a study on C4d deposition in IgAN on 29 selected patients was published in (doi: 10.12860/jnp.2015.04). Moreover, a gender-related differences in IgA nephropathy (doi: 10.34172/jnp.2023.21437; ethical code #IR.NIMAD.REC.1399.222) and finally a previous study was conducted on 238 biopsies (2009 to 2019) with particular focus on frequency of crescents in IgA nephropathy [doi: 10.34172/jpe.2020.14, ethical code #IR.MUI.MED.REC.1397.163, as the M.D. thesis of Maryam Rafieyan at the Isfahan University of Medical Sciences (Thesis# 397476)]. Furthermore, our group conducted a study on Ki-67 in IgAN [doi: 10.34172/ipp.2022.31369; ethical code #IR.NIMAD.REC.1398.067)], on a group of our biopsies between Jan 2020 and Jan 2021. The current study was conducted on 268 biopsy-proven renal biopsies and our longitudinal study will continue. This study protocol was registered on the Research Registry website with the unique identification number (UIN) [researchregistry9599](https://www.researchregistry.org/record/9599). The authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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