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The relationship between immun staining and progression markers in IgA nephropathy

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ABSTRACT

Objectives: To determine the relationship between immunofluorescence microscopy findings and progression markers at the time of diagnosis in immunoglobulin A (IgA) nephropathy.

Methods: Fifty-two patients with pathological diagnosis of primary IgA nephropathy by showing mesangial and mesangiocapillary IgA-dominant immune deposits in immunofluorescence microscopy were included in the study. At the time of biopsy, biochemical and hematological data, Oxford MEST score and immunofluorescent staining findings were recorded. The serum IgA/C3 ratio was calculated. The immunofluorescence results of the total group were compared with the markers of progression at the time of diagnosis, estimated glomerular filtration rate (eGFR), hematuria, proteinuria, creatinine, and serum IgA/C3 ratio.

Results: The mean age of the study group was 39.9±12.3 years and 55.8% were male. eGFR, albumin, hemoglobin, IgM were significantly lower, and uric acid and hematuria were significantly higher in those with proteinuria above 1 g compared to those with low proteinuria. A positive correlation was found between IgA, C3 and lambda staining and hematuria. There was a positive correlation between C3 staining and creatinine, and a positive correlation with hematuria. A correlation was found between Kappa staining and eGFR.

Conclusions: Correlation was found between IgA, C3 and lambda staining and hematuria at the time of diagnosis in IgA nephropathy.

Keywords: Immunoglobulin A nephropathy, immunostaining, hematuria

Immunoglobulin (IgA) nephropathy is the most common primary glomerular disease worldwide, but its geographic distribution varies greatly [1]. In addition to mild cases with abnormal urine findings, it shows a wide clinical spectrum in the form of rapidly progressive renal failure [2-4]. In a period of 20-30 years, end-stage renal disease develops in one third of the cases [5].

The Oxford classification is very important, as the prognosis and choice of treatment depend on the interpretation of the biopsy material. MEST score; M: mesangial hypercellularity (M0=<50%, M1=>50%), E: endocapillary hypercellularity (E0=absent, E1=present), S: segmental glomerulosclerosis (S0=absent, S1=present), T: tubular atrophy /interstitial fibrosis (T0=<25%, T1=26-50%, T2=>50%). An increase in total score during biopsy was found to be associated with poor prognosis [6, 7].

The complement system is an important component of innate and adaptive immunity and a comple-

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ment to antibody-triggered responses. Classical (C1), alternative (D, B, Properdin) and lectin (mannose-binding)-stimulated [8, 9]. IgA nephropathy (IgAN) is thought to arise due to autoimmunity involving abnormal activation of both alternative and mannose-binding lectin (MBL) pathways. MBL, an important protein in innate immunity, functions as a pattern recognition molecule to recognize carbohydrate patterns of microorganisms and activate complement via the lectin pathway.

After multiple adjustments, MBL deficiency IgAN was independently associated with poor outcomes [10]. Both local glomerular and systemic complement activation play a key role in the pathogenesis and clinical presentation. Serum complement levels are indicative of the degree of activation. The role of autoimmunity was emphasized in the most recent 4-hit hypothesis study [11-19]. Both IgA and C3 play important roles in IgAN pathogenesis [20].

The pathogenesis of light chains in glomerulopathies, where the main site of catabolism is kidney, is not clear. IgAN is characterized by increased plasma IgA1 levels and predominant mesangial polymeric IgA1 deposits. Increased binding of polymeric lambda IgA light chain to human mesangial cells may be responsible for disease immunity. Again, the production of IgA1 and IgA2 by mesangial cells may be a factor contributing to mesangial deposition [21].

It is still unclear whether the IF staining findings given alongside the Oxford classification have a predictive value [22]. IgA/C3 was expressed as a predictive biomarker [20, 23]. We planned to investigate the relationship between IF staining and progression markers eGFR, proteinuria, hematuria, creatinine and serum IgA/C3.

METHODS

Fifty-two cases diagnosed as primary IgAN because of mesangial and mesangial-capillary dominant immunofluorescent IgA deposition in kidney biopsy performed in our clinic between 2017 and 2020 were retrospectively included in the study. Those with secondary cause of IgAN were not included in the study. Demographic data such as age and gender at the time of biopsy, mean arterial pressure (MAP), urea, creatinine, estimated glomerular filtration rate (eGFR), albumin, hemoglobin, cholesterol, uric acid, serum IgG, IgA, IgM, C3, C4, IgA/IgG and IgA/C3 ratios, hematuria (>5 erythrocyte/hpf), leukocyturia (>5wbc/hpf), 24-hour urine proteinuria were recorded. eGFR was calculated with the CKD-EPI formula.

All kidney biopsies were evaluated by light and immunofluorescence (IF) microscopy. After the biopsy, the tissue, which quickly reaches the pathology unit in physiological saline, was frozen with snap-frozen in liquid nitrogen for IF, and 4µ sections were made. Sections were stained for at least 2 slides for IgG, IgA, IgM, C3, C1q, kappa and lambda. Pathology reports included IF staining between 0-3(+) and Ox-

Table 1. Demographic characteristics and laboratory result of the total group

Variables	n=52
Age (years)	39.88±12.34)
Gender, n (%)	
Females	23 (44.2)
Males	29 (55.8)
MAP (mmHg)	99.65±12.27
Laboratory	
Creatinine (mg/dL)	1.06 (1.46)
eGFR (mL/min)	76.0 (82.63)
Albumin (g/dL)	4.02 (0.60)
Hemoglobin (g/dL)	12.35 (2.33)
Cholesterol (mg/dL)	184.94±50.24
Uric acid (mg/dL)	6.07±1.72
IgG (mg/dL)	1134.55±385.24
IgA (mg/dL)	353.43±148.26
IgM (mg/dL)	107.29±52.32
C3 (mg/dL)	139.85±26.40
C4 (mg/dL)	32.77±10.05
Hematuria	18.0 (45.75)
Leukocyturia	3.0 (5.0)
IgA/IgG	0.31 (0.19)
Proteinuria	1431 (1925)

Data are shown as mean±standard deviation or median (interquartile range) or n (%). MAP=Mean arterial pressure, eGFR=estimated glomerular filtration rate, Ig=immunoglobulin, C=complement, Hematuria >5 erythrocyte/hpf, Leukocyturia=(wbc/hpf), proteinuria=mg/24 hours.

Table 2. Comparison of proteinuria ≥1g and proteinuria <1g diagnosed with IgAN

	Proteinuria ≥1 (n = 34)	Proteinuria <1 (n = 18)	Statistics (t, z or χ^2)	P value
Age (years)	41.52 ± 12.1	37.05 ± 12.5	1.250	0.217
Gender, n (%)			0.014	0.982
Females	15 (65.2)	8 (34.8)		
Males	19 (65.5)	10 (34.5)		
MAP (mmHg)	100.82±11.04	97.44±14.40	.943	0.350
Laboratory				
Creatinine (mg/dL)	1.52 (2.50)	0.96 (0.45)	-1.170	0.077
eGFR (mL/min)	56.0 (83.23)	90.80 (33.53)	-2.616	**0.009**
Albumin (g/dL)	4.04 (.87)	4.33 (0.41)	-2.646	**0.008**
Hemoglobin (g/dL)	11.87 (3.13)	13.25 (2.49)	-2.098	0.**041**
Cholesterol (mg/dL)	192.02±54.30	171.55±39.48	1.412	0.164
Uric acid (mg/dL)	6.41±1.78	5.42±1.43	2.037	**0.047**
CRP (mg/dL)	3.20 (10.59)	2.00 (6.57)	-2.213	**0.027**
IgG (mg/dL)	1099.8±404.3	1200.1±347.8	-0.892	0.377
IgA (mg/dL)	358.0±141.5	344.7±164.1	0.304	0.762
IgM (mg/dL)	95.9±40.2	130.5±64.7	-2.440	**0.018**
C3 (mg/dL)	136.9±27.0	145.3±25.0	1.148	0.257
C4 (mg/dL)	33.9±10.6	30.5±8.5	1.019	0.315
Hematuria (rbcs/hpf))	26.0 (45.0)	5.5 (19.7)	-2.040	**0.041**
Leukocyturia (wbc/hpf)	3.0 (5.0)	3.0 (5.75)	-0.481	0.630
IgA/IgG	0.35 (0.20)	0.29 (0.12)	-1.135	0.256
IgA/C3	2.68±1.19	2.40±1.12	0.813	0.420
Immunostaining				
IgA	3 (1)	3 (1)	-0.278	0.781
IgG	3 (1)	--	-1.873	0.061
IgM	0 (1)	0 (1)	-0.826	0.409
C3	2 (2)	2 (1.25)	-0.614	0.539
Kappa	0.0 (1)	1 (2)	-0.737	0.461
Lambda	1 (2)	1 (2)	0.246	0.805
MEST				
M	1 (0)	1 (0)	-0.48	0.962
E	1 (1)	0.5 (1)	-0.809	0.418
S	1 (0.25)	1 (1)	-1.152	0.249
T	1 (2)	0 (1)	-2.061	**0.039**

Data are shown as mean±standard deviation or median (interquartile range) or n (%). MAP=Mean arterial pressure, eGFR=estimated glomerular filtration rate, Ig=immunoglobulin, IgAN=IgA nephropathy, C=complement, CRP=C-reactive protein, Hematuria >5 erythrocyte/hpf, Leukocyturia=(wbc/hpf), M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy /interstitial fibrosis

ford-MEST scoring (pre-2017 scoring). M; Mesangial proliferation M0<50% or, M1>50%, E; Endocapillary hypercellularity E0=absent or E1=present, S; Segmental sclerosis S0=absent or S1=present, T; Tubular atrophy/interstitial fibrosis was evaluated as T0=0-25%, T1=26-50%, T2>50%. The other tissue piece was fixed with 10% formalin and 4µ sections were taken in paraffin blocks. Periodic acid Schiff was stained with hematoxylin eosin and trichrome. Results could not be given because C4d staining could not be performed routinely in our hospital. Pathology samples were evaluated twice. The IF results of the total group were compared with the progression markers, eGFR, hematuria, proteinuria, creatinine and IgA/C3, at the time of diagnosis. According to the C3 and IgA storage density, the categorical data as 0, +, ++, +++ were converted into numerical data as 0, 1, 2, and 3 positive. C3 storage was evaluated as<2+ and ≥2+.

The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 14.12.2022, Decision No: E-22-1145). Informed consent was obtained from all patients included in the study, which was conducted in accordance with the principles of Helsinki.

Statistical Analysis

Analyses were conducted using BM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA). All data were first checked for normality of distribution using the Kolmogorov-Smirnov and Shapiro-Wilk test. Normally distributed data are presented as the mean±standard deviation and others were represented as the median and inter-quartile range. Pearson chi-square and Fisher's exact test were used for categorical variables.

Table 3. Morphologic variables of Oxford-MEST classification.

n = 52	n	%
M (0/1)	3/49	5.8/94.2
E (0/1)	22/30	42.3/57.7
S (0/1)	15/37	28.8/71.2
T (0/1/2)	22/18/12	42.3/34.6/23.1

M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy/interstitial fibrosis

Spearman correlation was used for correlation analysis. Uni and multivariance regression analysis was used for factors affecting progression markers. P<0.05 was accepted as the significant level.

RESULTS

Demographic and laboratory data of 52 cases in total are presented in Table 1. Of 55.8% the cases were males, and the mean age was 39.9±12.3 years. Hypertension was seen in 8%, new onset diabetes mellitus in 3.8%., had no history of autoimmune disease.
When we evaluated the total group according to the rate of proteinuria, which is the most important marker of progression, those with proteinuria of 1 gram or more (65.3% of 34 cases) compared to those with less than 1 gram, e-GFR (z=-2.616, P=0.009), albumin (z=-2.646, P=0.008), serum IgM (z=-2.440, P=0.018) and hemoglobin (z=-2.098, P=0.041) were significantly lower, uric acid (t=2.037, P=0.047) and hematuria (z=-2.040, P=0.041) was found to be

Table 4. Frequency of deposited antibody intensity scores

Immunostaining	0	+	++	+++
IgA	0	2	16	34
IgG	46	3	1	1
IgM	35	12	4	1
C3	5	14	19	14
Kappa	27	13	11	1
Lambda	19	10	19	2

Ig = immunoglobulin, C = complement

Tablo 5. Relationship between immunofluorescent staining and progression markers

IF (n = 52)	IgA		IgG		IgM		C3		Kappa		Lambda	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
Creatinine	-0.033	0.81	0.193	0.170	0.003	0.981	0.270	**0.053**	-0.266	0.056	-0.283	**0.042**
eGFR	-0.027	0.847	0.142	0.317	-0.041	0.771	-0.226	0.107	0.325	**0.019**	0.226	0.107
Hematuria	0.403	**0.003**	0.208	0.138	-0.142	0.315	0.329	**0.017**	0.037	0.755	0.367	**0.007**
IgA/C3	0.134	0.343	0.044	0.758	-0.142	0.315	0.258	0.065	0.126	0.364	0.135	**0.**340
Proteinuria	0.008	0.955	0.213	0.129	0.165	0.241	0.098	0.488	-0.148	0.255	0.010	0.947

IF = immunofluorescent staining, eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, C = complement

significantly higher. There was no significant difference between mean arterial pressure, creatinine, hemoglobin, cholesterol, serum IgA and IgG, leukocyturia, IgA/IgG, IgA/C3, age and gender. There was no difference in IF staining between the groups. In comparison of MEST score, T score was found to be significant in the group with proteinuria ≥1g (z=-2.061, P=0.039) (Table 2).

The distribution of Oxford-MEST variables in the study group is given in Table 3, and the antibody density in the pathology samples is given in Table 4.
Correlation analysis of IF staining at the time of diagnosis and laboratory data revealed that there was a statistically significant positive correlation between C3 storage and creatinine in the total group (r=0.270, P=0.053). There was also a positive correlation between C3 storage and hematuria (r=0.329, P=0.017) and a positive correlation between IgA storage and hematuria (r=0.403, P=0.003). There was a positive correlation between lambda storage and hematuria (r=0.367, P=0.007), a negative correlation was found with creatinine (r=-0.283, P=0.042) and a positive correlation was found between kappa storage and e-GFR (r=0.325, P=0.019) (see Table 5).

No correlation was found between MEST score and serum IgA/C3 and IF findings. In binary regression analysis, in which we evaluated the effects of IF staining parameters on progression markers, it was determined that C3 storage had a borderline effect on creatinine. No significant effect was found between other IF staining parameters and progression markers (Table 6).

DISCUSSION

Diagnosis of IgA nephropathy is based on kidney biopsy in which immune deposits are shown in the glomerular mesangium in immunofluorescent microscopy [1]. Clinically, hematuria and proteinuria are important findings. Proteinuria was over 1 gram in 65.3% of the study group. In this group, hematuria and uric acid level were found to be significantly higher than the group with proteinuria less than 1 gram, while eGFR and albumin levels were significantly lower. These findings are closely related to progression and clinical outcome [2-5].

Since the prognosis and choice of treatment de-

Table 6. The binary logistic analysis of the predictors of the C3 staining in IgAN

Progression Markers	Exp(B)	95% CI for EXP(B)		P value
Creatinine	3,117	0,991	9,804	**0.052**
eGFR	1,033	0,998	1,070	0.670
Hematuria	0,999	0,993	1,005	0.821
IgA/C3	3,720	0,743	18,638	0.110
Proteinuria	1,000	1,000	1,000	0.382

eGFR = estimated glomerular filtration rate, Ig = immunoglobulin, IgAN = IgA nephropathy, C = complement

pend on the interpretation of the biopsy material, the Oxford classification, which expresses the morphological findings in light microscopic examination, is important [20]. According to data from previous studies, the degree of renal failure, morphological variants of the Oxford classification, and the degree of proteinuria were potential predictors of progression. In the study of Nasri *et al*. [24], there was no relationship between IgA, IgG, IgM and C3 immune stores, proteinuria and age. In this study, no relationship was found between IF findings and proteinuria and age. Again, the relationship between IgA deposition and MEST score with E and S, and IgM deposition with S was not found in our study. It was not found in our study, as was the case in the study, which showed that IgG deposition was not associated with the MEST score. We could not find the relationship between IgA and C3 deposition and E in our study. The relationship between C3 deposits and serum creatinine was found to be borderline correlation in our study. Although no relationship was found between IF and MEST score, the relationship between C3 storage and creatinine, one of the progression markers, shows the increasing importance of C3 storage [24, 28].

There may be other factors that can predict the progression and outcome of IgA nephropathy. It was presented that mesangial C3 deposition is an independent risk factor in progression and its role in the pathogenesis of complement activation [16, 21]. In recent studies, IgA/C3 ratio was also presented as predictive [17, 22, 23]. In our study, in which we investigated the relationship between IF staining intensity and progression markers in the light of these literatures, a positive correlation was found between C3 deposition and creatinine and hematuria immunohistologically. In the study by Nasri *et al*. [24], it was stated that the presence of C3 storage reached the endpoint more rapidly. In the study of Lang *et al*. [17], it was stated that serum IgA/C3 and glomerular C3 deposition may be useful markers of IgA nephropathy progression. In our study, a positive correlation was found between kappa deposition and e-GFR in the total group. Again, a positive correlation was found between IgA, C3 and lambda staining and hematuria. The correlation between IF staining and hematuria in the total group may reflect the fact that hematuria reported in epidemiological studies is a risk factor for proteinuria and that the level of hematuria is an independent indicator of progression to chronic kidney damage [21, 22, 25-27]. Initially, microscopic hematuria was associated with an 87% increase in the risk of end-stage renal disease, while macroscopic hematuria was associated with a 32% reduction [27].

The correlation between C3 storage and creatinine at the time of diagnosis appears to be compatible with the predictive value of C3 storage. The effect of C3 storage and creatinine in the regression analysis also supports this. [13, 28]. The positive correlation between IgA, C3, and lambda deposition and hematuria seem to contribute positively to the progression markers at the time of diagnosis in IgAN.

Limitations

The limitations of our study are that it is retrospective, single-center and the study group is small. Other limitations are the MEST score before 2017 and the inability to perform C4d staining in our pathology unit.

CONCLUSION

In order for IF staining to be used in IgA nephropathy,

the definition and reproducibility of immunofluorescence should be clarified. Does immunostaining have an independent prognostic value? Not known. The limited correlation between C3 storage and creatinine and the positive correlation between IgA, C3 and lambda storage and hematuria suggest that microscopic hematuria should be given importance in follow-ups in addition to proteinuria. More comprehensive studies are needed to elucidate the subject.

Ethics Committee Approval

The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 14.12.2022, Decision No: E-22-1145).

Authors' Contribution

Study Conception: SKŞ; Study Design: SKŞ, RB; Supervision: SKŞ, RB; Funding: SKŞ; Materials: SKŞ; Data Collection and/or Processing: SKŞ, RB; Statistical Analysis and/or Data Interpretation: SKŞ, RB; Literature Review: SKŞ, RB; Manuscript Preparation: SKŞ and Critical Review: SKŞ, RB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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