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Association of CD147 renal expression with morphologic lesions of Oxford classification in IgA nephropathy patients

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ABSTRACT

Introduction: Nephropathy of immunoglobulin A (IgA), is the most frequent glomerulonephritis worldwide. Nephropathy of IgA, has a highly variable course, either clinically or pathologically.
Objectives: The aim of this study was to assess CD147 expression with four morphological lesions of Oxford classification in IgA nephropathy patients.
Patients and Methods: The characterization of IgA nephropathy necessitated the existence of diffuse and global mesangial IgA deposition with weak C1q deposition. The kidney biopsies with the diagnosis of IgA nephropathy were included in the study. After the diagnosis of IgA nephropathy, four pathologic variables, of the Oxford classification of IgA nephropathy were assessed. For immunohistochemical staining, 4-µm-thick sections were stained with anti-human CD147 antibody. The intensity of CD147 staining on tubules, Bowman's capsules, vessels and tuft of glomeruli was expressed as percentage of involvement.
Results: In this study, 48 consecutive renal biopsies documented for IgA nephropathy were selected. Mean age of patients was 38.4±12.6 years. The average of proteinuria and serum creatinine were 1620.33± 720 mg/d and 1.33±0.54 mg/dL, respectively. We found vessels had the least and tubules had the highest mean of intensity of CD147 staining. This study showed that the intensity of CD147 staining in glomeruli was much higher among women than men. In addition, the association of T1 and T2 as the morphologic variables of Oxford classification with CD147 intensity staining on tubules was significant ($P=0.032$).
Conclusion: IgA nephropathy is common in various parts of the world. Beyond the Oxford classification, further work is still needed, to find other parameters having prognostic implication. Our study revealed some correlations of CD147; however, larger investigations are needed on this aspect of IgA nephropathy.

Implication for health policy/practice/research/medical education:
In a study on 48 renal biopsies of IgA nephropathy, we found, the association of T1 and T2 as the morphologic variables of Oxford classification with CD147 intensity staining on tubules was significant.
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Introduction

Immunoglobulin A (IgA) nephropathy can be considered as deposits of IgA in mesangial area of glomeruli or mesangiocapillary region, which may result in glomerular inflammation (1). Nephropathy of IgA, is the most frequent glomerulonephritis worldwide (1,2). Nephropathy of IgA, has a highly variable course, either clinically or pathologically. Clinical aspect of this disease may range from asymptomatic hematuria to a rapid course detected as a progressive glomerulonephritis (2,3). IgA nephropathy is mostly associated with the detection of microscopic hematuria or recurrent macroscopic hematuria (1-3). It is a benign disease in many patients. However, about 40% of IgA patients could finally achieve chronic renal failure

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and end-stage kidney failure (2-4). Morphologically, a spectrum of glomerular lesions can be detected. For instance, mesangial proliferation may be observed in almost all biopsies of most of the patients (with prominent IgA deposition). Moreover, other lesions like endocapillary hypercellularity and extracapillary proliferation and even severe necrotizing and crescentic glomerulonephritis may observe in some cases. Additionally, advanced glomerulosclerosis, interstitial fibrosis and tubular atrophy might be detected. Furthermore, numerous investigations have detected some clinical aspects having prognostic implication (2-5). Some parameters like proportion of proteinuria, progressive kidney dysfunction and male gender have prognostic implication (1,2). Studies regarding morphological lesions, as prognostic factors for development to end-stage kidney failure in nephropathy of IgA, have reported various findings (1-3). However, recently, four key morphological lesions were reported to be independently associated with kidney outcome (2-5). These pathologic lesions may include mesangial hyper-cellularity (M), hyper-cellularity of endocapillary region (E), segmental glomerulosclerosis (S) and interstitial fibrosis/tubular atrophy (T) which are known collectively as the MEST score or Oxford classification (2-5). Recently, a necessity for recognizing of some other specific markers to assess the progression of IgA nephropathy have been expressed. CD147, as a type I membrane glycoprotein has been presented by several cell types, comprising epithelial and endothelial cells. In normal renal tissue, CD147 is scattered in tubular epithelial cells and to a lesser intensity in glomerular components (6). The expression of CD147 is also significantly amplified in damaged renal proximal tubular epithelial cells. Additionally, it may be an important regulator in fibrosis of tubulointerstitial area. In fact, kidney fibrosis might be the main factor to have a prognostic implication of chronic progressive renal insufficiency (6,7). However, the clinical significance and morphological features of CD147 presentation in IgA nephropathy patients did not completely investigate and few studies had been published on this subject.

Objectives

The aim of this study was to assess CD147 expression with four morphological lesions of Oxford classification in IgA nephropathy patients.

Patients and Methods

Patients and specimens

All kidney biopsies with the diagnosis of IgA nephropathy were included in the study. Renal biopsies were collected from the patients who were referred to the renal pathology section of Baradaran laboratory located in Isfahan, Iran (2009 to 2017). None of patients was treated before the biopsy. Kidney biopsies with bellow than eight glomeruli were excluded from the study. In addition, none of the patients with diagnosis of IgA nephropathy had the history of liver disease, Henoch-Schönlein purpura nephritis, diabetic kidney disease, collagen vascular disease or any other systemic disease. Some important data were obtained at the time of biopsy include age, gender, serum creatinine and amount of proteinuria (based on a 24-hour urine collection).

Definition of IgA nephropathy

The pathological diagnosis of IgA nephropathy is straightforward. It is characterized by the existence of IgA-dominant or co-dominant immune deposits in mesangial or mesangiocapillary region of glomeruli, as demonstrated by immunofluorescence (IF) or immunohistochemistry. All renal biopsies were arranged for light and direct IF microscopy. For IF study, specific antibodies for human IgA, C1q, C3, IgG, IgM, and fibrin were used. The characterization of IgA nephropathy necessitated the existence of diffuse and global mesangial IgA deposition with weak C1q deposition (2,5).

Definitions of variables of Oxford classification

After IF diagnosis of IgA nephropathy, glass slides were histopathology studied to assess the four pathologic variables, which were presented in Oxford classification. The presence of mesangial (M0, M1), endocapillary hypercellularity (E0, E1), the proportion of tubular atrophy/interstitial fibrosis (IF/TA; T0, T1, T2) and segmental glomerulosclerosis (S0, S1) were evaluated based on the Oxford classification of IgA nephropathy. Additionally, data of Oxford classification was presented as MEST score which is a summation of all four variables (2,5).

Immunohistochemical analysis for CD147

For immunohistochemical staining, 4-µm-thick sections were stained with mouse monoclonal anti-human CD147 antibody [rabbit polyclonal to CD147; anti-CD147 antibody (ab64616; abcam)]. The intensity of CD147 staining on tubules, Bowman's capsules, vessels and tuft of glomeruli was expressed as percentage of involvement. In addition, a summation of intensity of CD147 staining [total intensity of CD147 (TI-CD147)] on all four mentioned elements was calculated for the analysis of possible correlation of total intensity of CD147 with other parameters.

Ethical issues

The study protocol was in accordance with the Declaration of Helsinki. This study was conducted on paraffin embedded blocks of renal biopsies to detect CD147. The ethical permission was obtained from the ethical committee of national institute for medical research development (NIMAD; http://nimad.ac.ir; Grant# 943613).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and differences between groups were

assessed by student *t* test or one-way ANOVA and followed by post hoc procedure (Bonferroni test). Categorical variables were stated as percentages and evaluated with Chi-square (χ^2) test. The reported *P* value was two-sided with a value of less than 0.05 as statistically significant criteria. All analysis had done by SPSS software version 22.0 (SPSS Inc, Chicago, Ill, USA).

Results

In this study, 48 consecutive renal biopsies documented for IgA nephropathy by IF and light microscopic studies were selected. Mean age of patients was 38.4 ± 12.6 years (minimum age; 15 years maximum age; 74 years). Around 28(58.3%) patients were male. The average of proteinuria and serum creatinine were 1620.33 ± 720 mg/d and 1.33 ± 0.54 mg/dL, respectively. Table 1 shows the mean of variables of Oxford classification and Table 2 shows the frequency distribution of CD147 intensity staining in areas of tubules, Bowman's capsules, vessels and tuft of glomeruli. Vessels (0.04 ± 0.29) had the least and tubules (33.02 ± 23.72) had the highest mean of intensity of CD147 staining (Table 2).

This study showed that the intensity of CD147 staining in glomeruli was much higher among women than men (2.85 ± 4.08 versus 0.50 ± 1.37; $P = 0.007$) (Table 3). CD147 staining tubules and TI-CD147 were also higher among women, but there were not statistically significant ($P > 0.05$).

Table 4 demonstrates the correlation between CD147 intensity staining (areas of tubules, Bowman's capsules, vessels and tuft of glomeruli) with proteinuria and serum creatinine. CD147 staining in vessels had direct significant association only with serum creatinine (r= 0.455, $P = 0.001$).

In addition, CD147 intensity staining did not have an association with age (in regions of tubules, Bowman's capsules, vessels and tuft of glomeruli) (Table 5).

Furthermore, the association of T1 and T2 as the morphologic variables of Oxford classification with CD147 intensity staining on tubules was significant ($P = 0.032$). Applying post hoc procedure (Bonferroni test), this significant association was due to the relation of T1 and T2 with CD147 staining on tubules ($P = 0.033$) but not with T0 (Table 6).

Table 1. Distribution of four variables of Oxford classification

Variable	Frequency	Percent
M		
M0	18	37.5
M1	30	62.5
Total	48	100
E		
E0	35	72.9
E1	13	27.1
Total	48	100
S		
S0	13	27.1
S1	35	72.9
Total	48	100
T		
T0	22	45.8
T1	18	37.5
T2	8	16.7
Total	48	100
MEST score		
0	6	12.5
1	5	10.4
2	16	33.3
3	12	25.0
4	6	12.5
5	3	6.3
Total	48	100

Discussion

To consider the intensity of CD147 staining with morphologic variables of IgA nephropathy and some demographic data, this study was conducted. This investigation showed that, vessels had the least and tubules had the highest mean of intensity of CD147 staining. In this study, also the intensity of CD147 staining in glomeruli was higher among women than men. Moreover, CD147 staining in vessels had a significant association with serum creatinine. Accordingly, the association of T1 and T2 as the morphologic variables of Oxford classification with CD147 intensity staining on tubules was significant. IgA nephropathy was detected as the most common form of glomerulonephritis throughout the world. In addition, around 30%–50% of individuals with IgA nephropathy extend to end-stage kidney failure within 20 years of onset of this disease. Importantly extensive kidney fibrosis and atrophy of the tubules are the major prognosticators of evolution to end-stage kidney failure. The glycosylated transmembrane protein CD147 is identified in the basolateral edge of tubular epithelial cells. However, it is not well-defined whether the presentation of CD147 associates with tubulointerstitial damage in IgA nephropathy patients. In a study conducted by Sun and colleagues on 86 renal biopsies from patients with IgA nephropathy, CD147 presentation was observed in the basolateral membrane of kidney cell tubules, while in normal renal specimens, positive staining for CD147 was not expressed in the renal tubular epithelial cells (6). They found a significant indirect correlation of CD147 staining of renal tubules with glomerular filtration rate. They also

Table 2. Frequency distribution of CD147 intensity staining in areas of tubules, Bowman's capsules, vessels and tuft of glomeruli

Variable	Min.	Max.	Mean	SD
Vessels	0	2	0.04	0.29
Bowman's capsule	0	30	1.04	5.15
Glomeruli	0	10	1.48	3.03
Tubules	3	80	33.02	23.72
TI-CD147*	3	140	41.63	32.61

*Total intensity of CD147.

Table 3. Association of the intensity of CD147 staining on tubules, Bowman's capsules, vessels and tuft of glomeruli with gender

Factors	Male Mean ± SD (number)	Female Mean ± SD (number)	*P* value
Vessels	0.07 ± 0.38 (28)	0 (19)	0.416
Glomeruli	0.50 ± 1.37 (28)	2.85 ± 4.08 (20)	0.007
Tubules	31.61 ± 23.66 (28)	35.00 ± 24.28 (20)	0.630
Bowman's capsules	1.79 ± 6.70 (28)	0 (20)	0.241
TI-CD147	39.32 ± 31.45 (28)	44.85 ± 34.73 (20)	0.568

TI-CD147; total intensity of CD147 of five mentioned elements.

Table 4. Correlation between CD147 intensity staining in areas of tubules, Bowman's capsules, vessels and tuft of glomeruli with proteinuria (g/d) and serum creatinine (mg/dL)

Factors	Proteinuria	Serum creatinine
	Correlation coefficient[b] (*P* value)	Correlation coefficient (*P* value)
Interstitial area	-0.155 (0.29)	-0.027 (0.85)
Vessels	0.077 (0.61)	0.455 (0.001)[a]
Glomeruli	-0.086 (0.56)	-0.096 (0.52)
Tubules	0.134 (0.36)	0.133 (0.37)
Bowman's capsules	0.106 (0.47)	-0.089 (0.55)
Score	0.038 (0.80)	0.066 (0.66)

[a] Significant at the 0.01 level (two-tailed).
[b] Positive means direct correlation and negative means inverse correlation.

reported a significant direct correlation of CD147 staining of renal tubules with serum creatinine and lesions of tubulointerstitial. However, the association found in this study, might be due to sample size of this study as a confounding factor. They also found, raised CD147 expression was associated with diminished kidney survival. Accordingly, an elevated CD147 immunostaining intensity as an independent predictor of kidney outcome among patients with IgA nephropathy was detected by Sun et al too. Finally, they concluded that CD147 presentation was accompanying with tubulointerstitial damage. Likewise they concluded that CD147 immunostaining intensity may predict kidney prognosis in IgA nephropathy, while CD147 may act as an early index for tubulointerstitial damage in IgA nephropathy (6).

More recently, Mori and colleagues considered the clinical significance of CD147 in biopsy-proven renal diseases which directed to the development of chronic renal failure (7). They conducted a cross-sectional study on 538 with various renal disease (mean age of 48.8 ± 17.3 years; 51.3% were females) and found the CD147 presentation in damaged lesions characterizing kidney inflammation. Similarly, plasma CD147 was associated with glomerular filtration rate among patients with inflammation-related renal diseases such as IgA nephropathy, Henoch-Schönlein purpura nephritis as well as diabetic kidney disease. In addition, in IgA nephropathy patients, plasma

Table 5. Correlation between the intensity of CD147 staining with age

Factors	Age (y)
	Correlation coefficient[a] (*P* value)
Interstitial area	0.071 (0.63)
Vessels	-0.109 (0.46)
Glomeruli	0.149 (0.31)
Tubules	-0.38 (0.80)
Bowman's capsules	-0.009 (0.95)
Score	0.015 (0.92)

[a] Positive means direct correlation and negative means inverse correlation.

Table 6. Correlation between CD147 intensity staining on tubules with variables of Oxford classification

Factors	Tubules Mean ± S.D. (number)	*P* value
M		
M0	30.67±22.55 (18)	0.60
M1	34.43±24.66 (30)	
E		
E0	36.09±24.63 (35)	0.14
E1	24.77±19.58 (13)	
S		
S0	33.31±25.47 (13)	0.96
S1	32.91±23.42 (35)	
T		
T0	30.68±20.02 (22)	0.032[a]
T1	27.22±22.84 (18)[b]	
T2	52.5±27.77 (8)[b]	
MEST Scores		
0	32.5±19.43 (6)	0.358
1	15±11.73 (5)	
2	38.62±25.12 (16)	
3	28.92±21.46 (12)	
4	44.17±30.73 (6)	
5	28.33±28.43 (3)	

[a] Significant; [b] Post-Hoc procedure (Bonferroni); significant (*P*=0.033)

CD147 values was associated with damaged regions (7).

Conclusion

IgA nephropathy is common in various parts of the world. Beyond the Oxford classification, further work is still needed, to find other parameters having prognostic implication. Our study revealed some correlations of CD147, however, larger investigations are needed on this aspect of IgA nephropathy.

Limitations of the study

The relatively low sample of renal biopsies could be a limitation of this study. We suggest further investigation on this feature of IgA nephropathy patients.

Authors' contribution

HN conducted the research. MR gathered the data. MA analyzed the data. HN and SM prepared the primary draft. MA edited the manuscript. HN and MA prepared the final paper. All authors read and site the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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