FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.8, No 1, 2001, pp. 19 - 25 UC 612.12

PROGNOSIS MARKERS OF TUBULOINTERSTITIAL INJURY IN PRIMARY TYPE I MESANGIOCAPILLARY GLOMERULONEPHRITIS

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Summary. *Renal fibrosis is the common pathway that leads to end-stage renal insufficiency in almost all renal diseases. Tubulointerstitial lesions are the basic parameter of progression in chronic glomerulonephritis. Tubular cells, as well as interstitial cells infiltrates, are of particular interest. A group of 32 patients (p) with primary type I mesangiocapillary glomerulonephritis (MCGN) was assessed concerning the relationship between the severity of the tubulointerstitial (Ti) lesions and blood pressure (BP), proteinuria and serum creatinine (SC). All p underwent kidney biopsies which were processed in light microscopy (LM-hematoxylin-eosin, Masson's trichrome, PAS), immunofluorescence, immunohistochemical (IH) procedures with monoclonal antibodies [performed with the EPOS-system, DAKO: -anti-smooth muscle cell actin (α-SMA); - anti-desmin (D), anti-cytokeratin (CK), anti-proliferating cell nuclear antigen (PCNA)]. The evaluation of the Ti lesions in LM revealed in 23 p (71.88%) severe Ti injury, which correlated significantly with the IH data: - the extent of the α-SMA positive cells (myofibroblasts) infiltrates (P<0.001), PCNA (P<0.01), D (proximal tubular necroses) (P<0.01), CK (distal tubular necroses) (P<0.001). Proteinuria correlated with α-SMA (P<0.001), PCNA (P<0.01), D (P<0.001), CK (P<0.001); SC correlated with α-SMA (P<0.001), PCNA (P<0.001), D (P<0.001), CK (P<0.01); BP did not correlate with these parameters.*
Ti lesions recorded in type I MCGN imply important myofibroblasts infiltrates and severe proximal and distal tubular involvement. These changes are consistent with the level of proteinuria and the rate of decline of renal function.

Key words: *Mesangiocapillary glomerulonephritis, myofibroblasts, proteinuria, renal fibrosis, tubular cells, tubulointerstitium*

Introduction

For several decades the mechanisms of progression of glomerular diseases towards chronic renal failure have been studied extensively. Recent research has cast light on the crucial role of renal fibrosis, as the final common pathway that leads to end-stage renal insufficiency in nearly all renal diseases. Attention has focused on the tubulointerstitial injury, which is the basic promoter of progression in chronic glomerulonephritis, as well as in non-glomerular diseases.

In chronic glomerulonephritis, the impairment of the glomerular permselectivity to macromolecules, with sustained protein trafficking through the nephron, results in enhanced tubular epithelial endocytosis of proteins and intracellular congestion, which, in turn, contribute to tubulointerstitial injury and renal scarring [1].

It has been postulated that apart from their many transport functions, tubular cells also secrete a vast array of cytokines, growth factors and vasoactive peptides. While glomerular injury may precede tubular injury, it is the latter that sets into motion the irreversible process of tubulointerstitial fibrosis, thus leading to loss of kidney structure and function [2]. Tubular cells are stressed by a number of cytokines, heavy proteinuria, ischaemia, toxins-like drugs or heavy metals. On the other hand, tubular cells are capable of expressing cytokines, adhesion molecules and extracellular matrix molecules that attract additional inflammatory cells to the interstitium [3,4].

There is a large body of evidence that highlights the primary importance of proteinuria in initiating and perpetuating tubulointerstitial damage. Proteinuria is the hallmark of glomerulonephritis responsible for the molecular basis of the events leading to the tubular and interstitial injury in glomerular diseases. Of the many consequences of heavy proteinuria, tubular epithelial cells involvement deserves a special attention.

More recently, up-regulation of interstitial fibroblasts function, triggered by molecules produced by injured tubular cells and interstitial infiltrating cells has been throughly documented [4]. Also, a possible link between tubular epithelial cells and interstitial fibroblasts has been forwarded. Many studies endorse the hypothesis that tubular cells might transdifferentiate into fibroblasts that, in the long run, change their phenotype into myofibroblasts, cells that express certain smooth-muscle proteins such as α-smooth muscle actin (α-SMA) and possess character-

istics of both fibroblasts and smooth muscle cells [5]. Their origin is still incompletely known, three potential sources being proposed: cortical [6] and medullary [7] fibroblasts, tubular cells [8,9] and pericytes [10]. The presence of α-SMA cells in the tubulointerstitium has been claimed as responsible for initiating and perpetuating renal fibrosis in experimental [11] and clinical glomerulonephritis [12]. Their possible role in the progression of renal interstitial fibrosis has been postulated in experimental studies in immune-mediated [8,13] and in non-immunologically induced renal diseases [14,15,16]. Progression towards chronic renal failure is strongly correlated with the extent of the tubulointerstitial involvement, fact demonstrated in mesangial proliferative glomerulonephritis, membranous glomerulonephritis, mesangiocapillary glomerulonephritis, diabetic nephropathy and renal amyloidosis.

In spite of having so many roles in renal fibrosis, far less studies have focused on tubular cells histologic prognosis markers and much more attention has been payed to myofibroblasts and macrophages that infiltrate the interstitium in the course of chronic glomerulonephritis.

The purpose of our study was to evaluate the role of the tubulointerstitial damage as prognostic indicator in patients with primary type I mesangiocapillary glomerulonephritis. From the practical standpoint, a particular interest has been directed towards the relationship between the tubulointerstitial histologic markers and proteinuria and renal function.

Subjects and methods

Study design

The study was conducted on a group of 32 patients with primary type I mesangiocapillary glomerulonephritis (MCGN). All patients were assessed concerning blood pressure, proteinuria and serum creatinine. Kidney biopsies were performed in all patients and specimens were processed as presented below. Blood pressure was determined in mmHg, proteinuria was evaluated by the Biuret method (g/24h) and serum creatinine was measured by standard autoanalyser technique Axsym (mg%).

Histology

Specimens of core needle biopsies were fixed in buffer formalin and embedded in paraffin. Five-micrometre paraffin sections were dewaxed, hydrated and stained with hematoxylin-eosin and Masson's trichrome staining methods.

Histochemistry

Additional sections were stained with the Gordon-Sweet silver staining method which identifies tubular and glomerular basement membranes in black.

Tubulointerstitial (Ti) lesions were evaluated on Masson's trichrome stained sections and were quantitated morphometrically by point count analysis. Renal biopsies were examined by the same pathologist, with a light microscope [a × 20 flat field objective (×200)]. A squared lattice of 25 points with a total surface area of 0.016 mm^3 was superimposed on the tissue and the data were collected from 10-12 adjacent fields along the biopsy specimen. Points falling on stained tissue were counted and their percentage of the total number of measured points was estimated [11,12,17].

Immunofluorescence (IF)

IF was performed in two-micrometre cryosections to reveal Ig deposits in the capillary loops and mesangium. Direct IF was undertaken with fluoresceine labelled rabbit anti-human Ig for IgG, IgA and IgM and rabbit anti-human C_3 (Cantacuzino Institute, Bucharest, Romania). Examinations were performed with a Nikon fluorescence microscope. A semiquantitative scoring scaled 0-4+ was used in order to appreciate the intensity of staining: no staining = 0; mild staining = 1; moderate staining = 2; strong staining = 3; severe staining = 4.

Immunohistochemistry

The immunohistochemical procedures were performed only in specimens fixed no longer than 24 hours.

Three-micrometre sections from each case were immunostained with the following antibodies provided by Dako Ltd., Glostrup, Denmark:

- Anti-smooth muscle cell actin, Clone 1 A_4 - highly specific for α-smooth muscle actin (α-SMA);
- Anti-vimentin (V), Clone Vim 3 B_4;
- Anti-proliferating cell nuclear antigen (PCNA), Clone PC-10, which recognizes cells in G_1, S and G_2 phases;
- Anti-desmin (D), Clone D_{33};
- Anti-cytokeratin (CK), Clone MNF 116.

The visualization of the final reaction product was performed with diaminobenzidine dyhidrochlorid (DAB). All immunoreactions were performed with the EPOS system, introduced in practice by Dako.

Labelled cells in tissue sections were evaluated as described at the evaluation of histological Ti injury. Data related to Ti α-SMA^+, D^+, CK^+ and $PCNA^+$ cells are presented as means ±SD per glomerular cross-section and scored as follows: *α-SMA*: 0 = no immunostain for interstitial myofibroblasts; 1 = 1-2 peritubular myofibroblasts; 2 = 3-5 peritubular myofibroblasts; 3 = >5 myofibroblasts present in the medular and cortical areas, as well as in the peritubular and periglomerular areas; *PCNA*: 0 = absent; 1 = 5%; 2 = 5 - 15%; 3 = >15% stained nuclei; *D*: 3 = all proximal tubule (PT) cells stained; 2 = 1-2 focal necroses / PT; 1 = >3 necroses / PT; 0 = PT not stained (global necroses); *CK*: 3 = all collecting and distal tubule (C - DT) cells stained; 2 = 1-2 focal necroses / C - DT; 1 = > 3 necroses / C-DT; 0 = C-DT not stained (global necroses).

Statistical analysis

Clinical, biochemical, histological and immunohistochemical data were evaluated by statistical methods using the EPI INFO 6, INSTAT and EXCEL statistical packages: the comparison between clinical, biochemi-

cal, histological and immunohistochemical data (expressed as means ±SD) was performed by the unpaired Student's t-test; the correlations between the histological and immunohistochemical data were performed by the non-parametric Spearman's rank order test; the correlations between the clinical, biochemical and immunohistochemical data were performed by the parametric single Pearson's test.

Correlation coefficients (r_s and r values, respectively) of the linear regression analyses are presented in relationship with P values. Statistical significance was considered as $P<0.05$ and weak significance was accepted as $0.01<P<0.02$.

Results

Assessment of the clinical, biochemical, histological and immunohistochemical data.

A comparison between the abovementioned parameters is presented in Table 1 (group II of patients represents 71.88% of the total number of patients and was remarkable for its very severe Ti lesions).

Histology

Of the 32 patients with primary, type I MCGN, group I (9p – 28.12%) had a slight involvement of the tubulointerstitium, which showed minor tubular lesions and a mild interstitial mononuclear cells infiltrate. On the contrary, group II (23p – 71.88%), presented with severe Ti lesions and a severe interstitial infiltrate, which consisted of macrophages, lymphocytes and fibroblasts.

The correlation between the histological and immunohistochemical data in groups I and II is presented in Table 2.

Table 2. Correlation between histological and immunohistochemical data in groups I and II

		Tubulointerstitium			
		α-SMA	PCNA	D	CK
Group I	TI %	* 0.51	0.08	–0.13	–0.11
Group II	TI %	*** 0.98	** 0.61	** -0.64	*** –0.83

Immunohistochemical index for interstitial α-SMA and PCNA, for proximal tubular desmin (D) and for distal tubular cytokeratin (CK) cells was compared with the TI histological index by the non-parametric Spearman's rank order test. Correlation coefficients (r_s values) are presented in relationship with P values (* P<0.05; ** P<0.01; *** P<0.001).

Table 3. Correlation between clinical, biochemical and immunohistochemical data in group I

Group I	Tubulointerstitium			
	α-SMA	PCNA	D	CK
BP (mmHg)	0.12	0.08	0.08	0.11
P (g/24h)	* 0.41	0.11	–0.12	–0.07
SC (mg%)	** 0.48	0.19	–0.14	** –0.53

Immunohistochemical index for interstitial α-SMA and PCNA, for proximal tubular desmin (D) and for distal tubular cytokeratin (CK) cells was compared with the clinical and biochemical data by the parametric single Pearson's test. Correlation coefficients (r values) are presented in relationship with P values (* P<0.05; ** P<0.01; *** P<0.001).

Table 4. Correlation between clinical, biochemical and immunohistochemical data in group II

Group II	Tubulointerstitium			
	α-SMA	PCNA	D	CK
BP (mmHg)	0.12	0.08	0.13	0.18
P (g/24h)	* 0.79	* 0.67	** –0.71	** –0.73
SC (mg%)	** 0.88	** 0.79	** –0.85	* –0.66

Immunohistochemical index for interstitial α-SMA and PCNA, for proximal tubular desmin (D) and for distal tubular cytokeratin (CK) cells was compared with the clinical and biochemical data by the parametric single Pearson's test. Correlation coefficients (r values) are presented in relationship with P values (* P<0.05; ** P<0.01).

Immunohistochemistry

α - *Smooth-muscle actin (α-SMA)*

α - Smooth-muscle actin *(α-SMA)* was detected within the media of renal arterioles, glomeruli and interstitium. The glomerular immunostain was confined only to mesangial cells in a granular pattern and did not involve epithelial or endothelial cells (as presented in a previous work – 18)

α-*SMA* expression was noted in a diffuse pattern in the peri-glomerular and peritubular areas, as well as in the interstitium and α-*SMA* $^+$ cells were identified as myofibroblasts infiltrates.

In group I, the Ti lesions correlated directly with the interstitial α-*SMA* ($r_s = 0.51$; $P<0.05$), while in group II, the Ti lesions correlated strongly with the interstitial α-*SMA* ($r_s = 0.98$; $P<0.001$).

Proliferating cell nuclear antigen (PCNA)

Proliferating cell nuclear antigen (PCNA) was expressed by α-*SMA*$^+$ mesangial cells within the glomerulus and by α-*SMA*$^+$ peritubular and interstitial cells. In

Table 1. Comparison between clinical, biochemical, histological and immunohistochemical data in groups I and II

Patients	BP (mmHg)	P (g/24h)	SC (mg%)	Tubulointerstitium				
				TI %	α-SMA	PCNA	D	CK
Group I	141.60±21.50	3.71±1.65	0.84±0.21	11.33±3.35	1.44±0.52	1.22±0.44	1.67±0.60	2.88±0.33
Group II	149.31±21.06	** 6.73±2.13	*** 3.44±3.72	*** 21.73±8.55	*** 2.47±0.73	*** 2.08±0.73	* 1.82±1.07	*** 1.65±0.92

Unpaired Student's t-test (* P<0.05; ** P<0.01; *** P<0.001); data are expressed as means ± SD; BP - blood pressure; P - proteinuria; SC - serum creatinine; TI - tubulointerstitium; α-SMA - α smooth muscle cell actin; PCNA-proliferating cell nuclear antigen; D-desmin; CK-cytokeratin.

group I, this index did not correlate with the Ti lesions, while in group II, the Ti lesions correlated directly with the interstitial $PCNA^+$ cells ($r_s = 0.61$; $P<0.01$).

Vimentin (V)

Vimentin immunostain was detected in mesangial cells and it appeared neither within visceral epithelial and endothelial cells, nor within peritubular, tubular and interstitial cells (as described in a previous work – 18).

Desmin (D)

Desmin stained normal proximal tubular cells and was a sensitive marker that detected focal tubular necroses in early stages of tubular impairment. Ti lesions correlated inversely with the D immunostain ($r_s = –0.64$; $P<0.01$). Also, D stained very few postmitotic myofibroblasts, sparsely distributed in the peritubular areas.

Cytokeratin (CK)

Cytokeratin stained normal distal and collecting tubular cells and was a sensitive marker for focal tubular necroses. CK also stained few glomerular epithelial cells. In group II, Ti lesions had an inverse correlation with the CK immunostain ($r_s = –0.83$; $P<0.001$).

The clinical, biochemical and immunohistochemical data were correlated in both groups as presented in Tabel 3 and 4 (Pearson's test). Blood pressure did not correlate with the immunohistochemical aspects, neither in group I, nor in group II.

In group I, proteinuria correlated directly weakly with the interstitial α-*SMA* ($r = 0.41$; $0.01<P<0.02$) and showed no correlation with the tubular D and CK immunostain. In the same group, serum creatinine correlated directly with the interstitial α-*SMA* ($r = 0.48$; $P<0.05$), but did not correlate with the tubular D and CK stainings.

On the contrary, in group II, proteinuria had a strong direct correlation with the interstitial α-*SMA* ($r = 0.88$; $P<0.001$) and PCNA ($r = 0.79$; $P<0.001$). Also, proteinuria had a significant indirect correlation with the proximal tubular D ($r = –0.71$; $P<0.001$). Serum creatinine correlated directly with the interstitial α-*SMA* infiltrates ($r = 0.88$; $P<0.001$) and PCNA ($r = 0.79$; $P<0.001$), and showed an inverse correlation with the proximal tubular D ($r = –0.85$; $P<0.001$) and the distal tubular CK ($r = –0.66$; $P<0.01$).

Immunohistochemical aspects evidenced in group II are presented in Fig 1, Fig 2 and Fig 3.

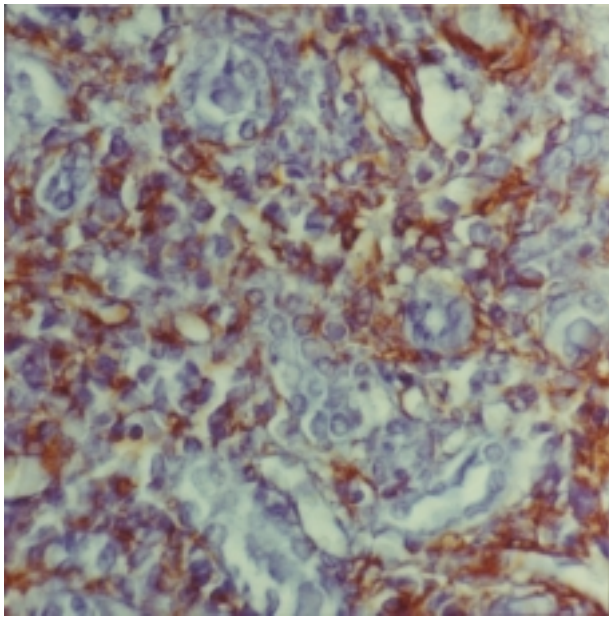

Fig 1. Immunohistochemistry showing α-SMA expression (brown stain) within the interstitium and peritubular areas. Magnification ×400.

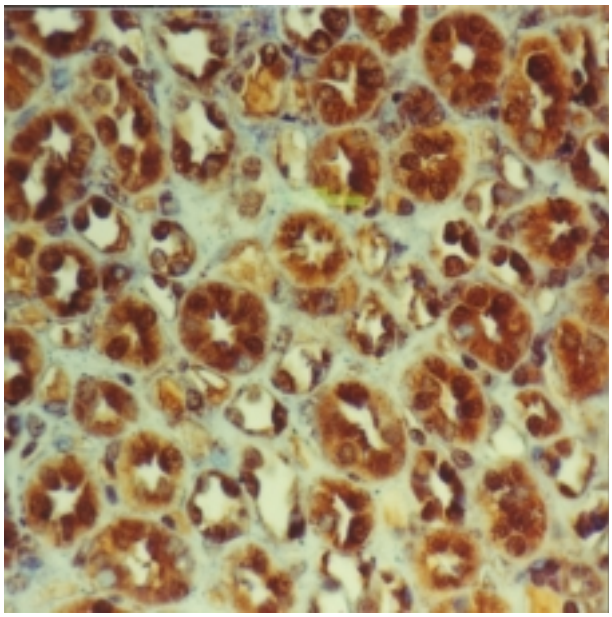

Fig 2. Immunohistochemistry showing proximal tubules (PT) stained with desmin (brown staining). Focal necroses are revealed by the absence of staining in PT cells. Magnification ×400.

Discussion

The results of this study show a significant tubulointerstitial injury in the histological features of primary type I MCGN. The biochemical picture, as well as the histological parameters that evaluate the tubulointerstitial involvement, are far more severe in patients with immunohistochemical markers of tubular and interstitial impairment.

Proteinuria correlated significantly with the distribution of α-*SMA* / PCNA positive cells, identified as proliferating myofibroblasts, encountered within the periglomerular and peritubular areas, and the interstitium. These cells were organized in the periglomerular areas, giving the aspect of a "pseudo-capsule" and surrounding glomeruli with advanced aspects of glomerulosclerosis.

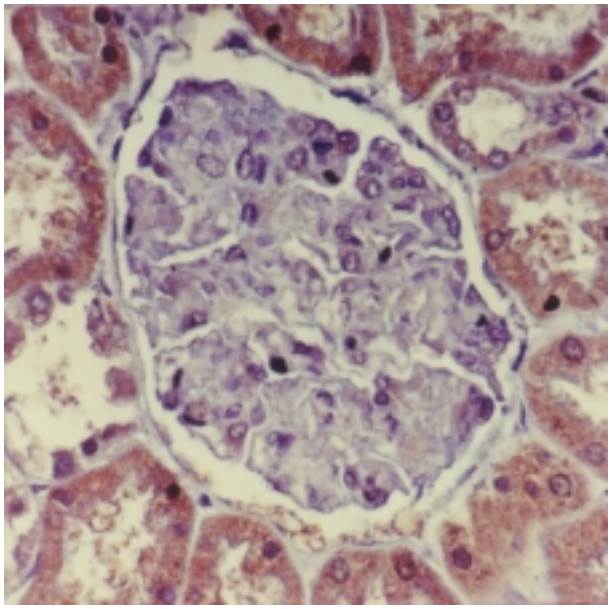

Fig 3. Immunohistochemistry showing distal tubules (DT) stained with cytokeratin (brown staining). Focal necroses are revealed by the absence of staining in DT cells. Sparse glomerular visceral epithelial cells stained with cytokeratin. Magnification ×400.

The relevance of periglomerular myofibroblasts in the progression of glomerulonephritis has been discussed in several works. The authors describe interstitial myofibroblasts that appear predominantly surrounding Bowman's capsule and tubules at early stages of glomerular disease. Periglomerular myofibroblasts appeared surrounding the nonsclerotic hypertrophic glomeruli, which may lead finally to glomerulosclerosis. These aspects suggest that interaction between the glomerular cells and the periglomerular myofibroblasts may have a role in the progression of glomerular disease [19].

Several studies underline the fact that these immunohistological findings might predict the outcome of chronic glomerulonephritis. It has been generally assumed that amongst other factors perpetuating damage and progression of chronic renal failure, severe interstitial myofibroblasts infiltrates are an important hallmark of renal fibrosis and, thus, they predict a poor outcome of glomerulonephritis. The appearance of α-SMA positive myofibroblasts within the tubulointerstitium is a characteristic of interstitial fibrosis in many types of glomerulonephritis, such as IgA nephropathy [12,20], membranous glomerulonephritis [21,22], mesangiocapillary glomerulonephritis [23,24].

In addition, it is worth pointing out that renal function assessed by serum creatinine was significantly impaired in patients with extended tubulointerstitial lesions, mainly with severe myofibroblasts infiltrates, changes also found in the studies of Adam et al and Dobronravov in mesangiocapillary glomerulonephritis [23,24]. Bohle et al suggested in their works that progressive renal failure is seldom recorded in patients who do not present severe tubulointerstitial changes [25].

Another important issue would be the evaluation of specific histologic markers of tubular damage. In our study, desmin, which disclosed severe proximal tubular necroses, and cytokeratin, which revealed extended distal tubular lesions, correlated strongly with proteinuria and the severity of renal function impairment.

It is of note that other studies did not describe desmin expression within the diseased tubules [11,17,24]. Also, surprisingly, the studies of Adam et al, as well as those of Muchaneta-Kubara et al and Essawy et al, revealed expression of vimentin by atrophic tubular cells, fact not demonstrated in our study [14,17,24].

The same authors describe desmin expression displayed strongly by glomerular visceral epithelial cells in experimental renal scarring [14] and in diabetic nephropathy [17], aspects not encountered in our patients.

Under these circumstances, one might assume that desmin, as cytoskeletal protein, is expressed by various types of cells (epithelial cells, mesangium, tubules, postmitotic myofibroblasts), expression which is dependent on certain circumstances, such as hypertension, heavy proteinuria [14]. Desmin is the most sensitive marker to reflect the functional state of the organ sclerosis effective cell system from the resting to the activating state [26].

It is worthwhile menitioning that not only did poor desmin expression by proximal tubules correlate with proteinuria and renal function, but it also correlated with the extension of the peritubular myofibroblasts infiltrates. This is in keeping with other studies that underline a paracrine stimulation of human renal fibroblasts by proximal tubule cells, via TGF_{β} and PDGF-AB secreted by the tubule cells. Renal insults that result in proximal tubule injury may perturb this paracrine interaction, thereby culminating in excessive fibroblast proliferation and interstitial fibrosis [27].

As for the distal tubular cells, they displayed severe necroses revealed by impaired expression of cytokeratin, which correlated significantly with proteinuria, renal function and the interstitial myofibroblasts infiltrates. According to Goto et al, cytokeratin immunoreactivities are almost exclusively detected in normal epithelial cells of Henle's loops and collecting ducts, and far less in proximal and distal tubules. This observation maintains the idea that cytoskeletal or α-SMA and other intermediate filaments vary in distribution in different segments of renal tubules and represent a histologic marker of segmental differentiation of renal tubules functions [28].

Furthermore, glomerular expression of cytokeratin was encountered in the glomerular epithelial cells in diseased glomeruli in the course of chronic glomerulonephritis [28,29], fact also described in our study.

At present, an undeniable link between tubules and their involvement in the process of tubulointerstitial fibrosis is proteinuria, which triggers all the abovementioned tubular and interstitial changes. It has been pro-

posed that filtered proteins cause interstitial inflammation and scarring by damaging the tubules through complex and concurrent mechanisms such as lysosomal rupture, ammonia production, hypoxia and release of chemoattractants, cytokines and extracellular matrix proteins. These processes lead to accumulation of macrophages, which in turn recruit and stimulate fibroblasts [2,30,31].

To date, tubular epithelial cells, especially those of proximal tubules are proven to play a dynamic role in the pathogenesis of tubulointerstitial fibrosis. Briefly, the main mechanisms that contribute to tubule cell activation are: - the direct involvement by primary disease process; - activation by glomerular-derived cytokines that reach tubule cells via the urine space, vasa recta or diffusion through interstitial space; - injury by plasma proteins filtered in excess as a consequence of injury to the glomerular filtration barrier; - ischaemia downstream to glomerular injury; - hyperfunction of remnant tubules [4,32].

In the long run, these mechanisms result in severe consequences that become deletorious and promote progression of chronic renal failure. The molecular basis of the events responsible for the tubulointerstitial injury is represented by processes that act concomitantly or sequentially: - release of cytokines, complement components and other inflammatory mediators; - up-regulation of fibroblast function, leading to its transdifferentiation into myofibroblast; - increased synthesis of extracellular matrix proteins by activated fibroblasts, interstitial macrophages and tubular cells; - loss of tubule cellularity by excessive apoptosis that limits the kidney to remodel and repair after injury, thus promoting tubulointerstitial fibrosis [1,4,32,33,34].

These data support the ideea that significant damage to cortical tubulointerstitium occurs concurrently with glomerular injury in primary glomerulopathies and may predict the clinical course of the disease, already in its initial phase [35].

In conclusion, our study reveals significant tubular and interstitial lesions in the histologic features of primary type I mesangiocapillary glomerulonephritis. These tubulointerstitial lesions imply important myofibroblasts infiltrates and severe proximal and distal tubular involvement. Of interest, these changes are consistent with the level of proteinuria and the rate of decline of renal function. Also, we assume that the immunohistological methods that assess prognosis markers, such as α-SMA, desmin and cytokeratin expression, are a reliable tool in the evaluation of primary type I mesangiocapillary glomerulonephritis and, therefore, should be used on a regular basis.

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PROGNOSTIČKI MARKERI TUBULOINTERSTICIJSKOG OŠTEĆENJA U PRIMARNOM MEZANGIOKAPILARNOM GLOMERULONEFRITISU TIP I

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Kratak sadržaj: *Fibroza bubrega je čest proces koji vodi u terminalnu uremiju u većine bubrežnih bolesti. Tubulointersticijsko oštećenje je osnovni parametar u progresiji hroničnog glomerulonefritisa. Od posebnog interesa su tubulske ćelije i intersticijski infiltrati ćelija. Ispitivana je grupa od 32 bolesnika sa mezangiokapilarnim glomerulonefritisom tip I (MCGN) i ispitivan odnos između težine tubulointersticijskih promena sa krvnim pritiskom, proteinurijom i serumskim kreatininom. U 23 bolesnika (71,88%) nađeno je teško tubulointersticijsko oštećenje koje je koreliralo značajno sa stepenom infiltracije α-SMA pozitivnih ćelija (miofibroblasta) (P<0,001), PCNA (P<0,01), anti-desminom (nekroza proksimalnih tubula) (P<0,01), anticitokeratinom (nekroza distalnih tubula) (P<0,001). Proteinurija je korelirala sa α-SMA (P<0,001), PCNA (P<0,001), anti-desminom (P<0,001), anti-citokeratinom (P<0,01). Krvni pritisak nije korelirao sa ovim parametrima.*
U zaključku, oštećenja nađena u MCGN ukazuju na značajnu infiltraciju miofibroblasta i teška oštećenja proksimalnih i distalnih tubula. Ove promene odgovaraju stepenu proteinurije i stepenu smanjenja bubrežne funkcije.

Ključne reči: *Mezangiokapilarni glomerulonefritis, miofibroblasti, fibroza bubrega, tubulske ćelije, intersticijum bubrega*