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C3 Depositions in Proximal Tubular Epithelial Cells are Common in Minimal Change Disease and in IgM Nephropathy

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Abstract

Background. Tubulointerstitial damage is a consistent feature of progressive glomerular injury. The aim of the study was to establish the incidence of C3 depositions in proximal tubular epithelial cells (C3 PTEC) and to evaluate the role of proteinuria (Pu) for these changes.
Methods. We reviewed 94 kidney biopsies provided for 1 year in our clinic for deposition of C3 in proximal tubular epithelial cells (PTEC).
Results. C3 PTEC were established at 16 of them (17,02%). Five (7,08%) from all patients with mild and moderate Pu and 11 patients (36,67%) from those with nephrotic Pu had such findings. From 16 patients with C3 PTEC-8 (50%) were with idiopathic nephrotic syndrome-4 with minimal change disease and 4 with IgM nephropathy, 2 were with IgA nephropathy, 2 with interstitial nephritis, 1 with crescentic, 1 with membranous and 1 with membranoproliferative glomerulonephritis. Mean Pu was 5,36±5,3g/d. Serum creatinine was 197±120,21 μmol/l and creatinine clearance was 53,2± 25,03ml/min/1.73m2. With C3 PTEC were 11 patients (68,75%), with Pu 10,5±3,4g/d and 5 (31,25%) were with 1,26±0,9g/d. There was a correlation between duration of hypertension and C3 PTEC /r=+0,774, p<0,01/.
Conclusion. We conclude that C3PTEC are rarely findings in kidney biopsy. Their incidence is higher in patients with massive Pu and are common in patients with minimal change disease and IgM nephropathy.

Keywords: glomerulonephritis, tubulointerstitial chan-ges, morphology, proximal tubular epithelial cells, C3 deposition, proteinuria

Introduction

Tubulointerstitial damage is a consistent feature of progressive glomerular injury. However, the mechanisms by which inflammatory events in the glomerulus involve the tubulointerstitium remain poorly understood. Recent data suggest that proximal tubular epithelial cells (PTEC) are important in the mediation of that process. They interact with a wide range of urinary products and their response to these products may promote tubulointerstitial damage [1]. Complement proteins and their activation products may reach the PTEC *via* the glomerular filtrate, especially during states of non-selective proteinuria. They are also produced locally by the PTEC and other cells in the kidney [2,3]. Some authors suggested that renal tubular synthesis of C3 and its activation in the cortical interstitium is a mechanism for the progression of glomerulonephritis to interstitial injury [4]. Experimental studies with rats indicated that in primary mesangio proliferative glomerulonephritis with proteinuria, the development of tubulointerstitial lesions is associated with activation of serum complement at the level of tubular brush border, and tubulointerstitial lesions can be reduced by inhibition of complement activity [4]. Proteinuria can induce tubulointerstitial injury by several mechanisms. High protein concentrations in tubular fluid, can be toxic for tubular cells by leading to lysosomal swelling or obstructing tubules with proteinaceous casts. Specific proteins that have been reported to be cytotoxic include transferrin and lipoproteins, which can generate oxidants or chemotactic factors.[5,6,7,8]. Although complement activation and deposition have been associated with a variety of glomerulopathies, the pathogenic mechanisms by which complement directly mediates renal injury remain to be fully elucidated.
The aim of the study was to establish the incidence of C3 depositions in proximal tubular epithelial cells (C3 PTEC) and to evaluate the role of proteinuria (Pu) for these changes

Patients and methods

We reviewed all 94 kidney biopsies, that were performed in 2007 in Nephrology Clinic of University Hospital "Queen Joanna – ISUL" for C3 PTEC. Such immune depositions were found in 16 patients (17.02%), as the ratio men/women were 10/6, mean age 46,1±13,5 years. We followed up: proteinuria, serum albumin, serum creatinine, uric acid; creatinine clearance, calculated with Cockcroft-Gault, urine sediment, duration of disease and hypertension before kidney biopsy, systolic and diastolic blood pressure (BP). These data were compared with morphological changes in kidney biopsies. The

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samples from kidney biopsies were examined by light and immunofluorescence microscopy. The intensity of mesangial proliferation and matrix expansion were graded semiquantitatively on a scale from 0 to 2+, where 0 was absent and 2+ was diffuse. The intensity of immune deposition was graded semiquantitatively on a scale from 0 to 4+, where 4+ meant high intensity. The stage of chronic kidney disease was classified according to K/DOQI classification.

Statistical methods

Data are presented as mean±SEM. Correlation were assessed by regression using software package for Microsoft Excel. P values <0,05 were considered significant.

Results

Among all 94 patients proteinuria was mild to moderate in 64 from them and 30 had Pu more than 3.5 g/d. The deposition of C3 PTEC was observed in 5 (7,81%) patients from the first group and in 11 (36,67%) from the second group (p<0,01) (Figure 1).

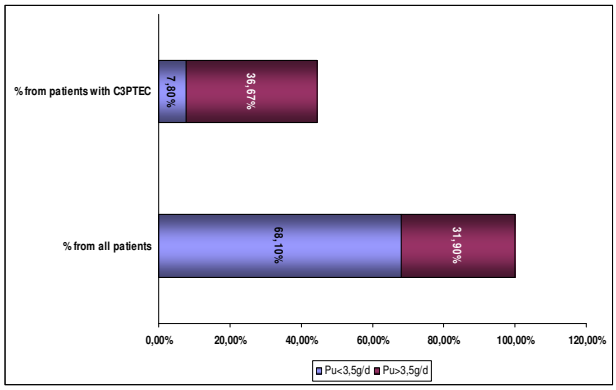

Fig.1. Patients with C3PTEC according to the proteinuria

According to morphological diagnosis C3 PTEC were most often in patients with idiopathic nephrotic syndrome – 8 patients (50%)-four of them with minimal change disease and 4 with IgM nephropathy. Two patients were with chronic interstitial nephritis, two-with IgA glomerulonephritis, one was with crescentic glomerulonephritis, 1-with membranous glomerulonephritis, 1-with amyloidosis and 1 with mesangiocapillary glomerulonephritis (MCGN) (Figure 2).

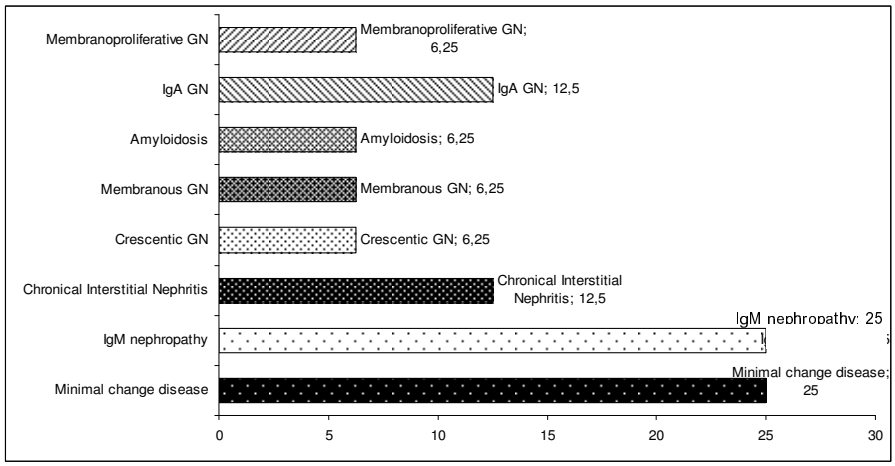

Fig. 2. Percentage of patients with C3PTEC according to the morphological diagnosis

Duration of the disease before kidney biopsy in patients with C3PTEC was 10,3±11,6 months. (from 1 to 36 months). With hypertension were 12 patients (75%) from that group. Duration of high blood pressure was 31,5±13,5 months. (from 3 to 120 months). Systolic blood pressure was 137,2±21,4 mmHg and diastolic blood pressure was 87,2±10,94 mmHg. There was a correlation between the duration of hypertension before kidney biopsy and C3 PTEC (r= +0,774, p<0,01).

Proteinuria in all patients with C3 PTEC was 5,36±5,3 g/d. In the group of patients with mild to moderate protein excretion it was 1,26±0,9 g/d, while in the group with nephrotic range Pu it was 10,5±3,4 g/d (p<0,001).

All patients had a decreased GFR and were classified from 2 to 4 grade of CKD, according to K/DOQI classification. With stage 2 were 8 patients, with stage 3 were 3 patients and with stage 4 were 5 patients. Serum creatinine was 197±120,21µmol/l and creatinine clearance was 53,2±25,03ml/min/1.73m^2. Ten patients (62,5%) were with increased levels of serum creatinine, 6 of them were with nephrotic range Pu, while 4 (40%) were with protein loss in the urine less than 3,5 g/d (p<0,05). Five patients (31,25%) were with massive Pu with normal serum creatinine and only 1 patient (6,25%) was with protein excretion below 3,5 g/d and normal levels of serum creatinine.

There was no correlation between the stage of chronic kidney disease, serum creatinine and creatinine clearance with intensity of C3PTEC (resp r=-0,05; r=-0,121; r=-0,129). We did not establish correlation between C3PTEC and Pu (r=+0,300, p>0,05).

In data analysis we observed pronounced hypoalbuminemia with dyslipidemia. Nine patients were with hypoalbuminemia and 8 were with hypercholesterolemia, six – with hypertriglyceridemia and eight – with hyperuricemia. (Table 1).

Table 1. Laboratory data at the time of kidney biopsy in patients with C3 PTEC

Parameter	Value
Serum albumin [g/l]	32,7±10,45
Total Cholesterol [mmol/l]	8,1±2,99
Triglycerids [mmol/l]	2,62±1,63
Uric acid [µmol/l]	371±121,3

The morphological changes from kidney biopsy are shown on Table 2. The majority of patients were with tubular and interstitial changes. The intensity of C3PTEC were most frequently moderate- in 11 patients (68,75%). C3 PTEC were single findimg in 5 patients, while at the others they were combined with immunoglobulins. (Figure 3). The intensity of C3PTEC did not correlate with the morphological changes in the kidney biopsies.

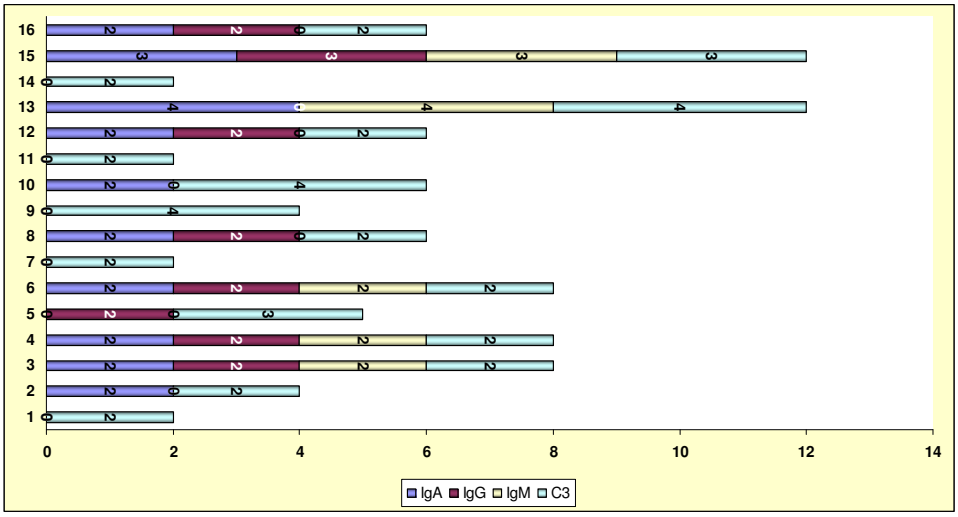

Fig. 3. Depositions of C3 and other immunoglobulins in PTEC

Table 2. Morphological changes in patients with C3 PTEC

Morphological changes	Number of patients (%)
Sclerotic glomeruli	5 (31,25%)
Mesangial cell proliferation	14 (87,5%)
Enlarged mesangial matrix	15 (93,75%)
Crescents	2 (12,5%)
Interstitial infiltrates	12 (75%)
Interstitial fibrosis	12 (75%)
Tubular dystrophy	11 (68,75%)
Tubular atrophy	11 (68,75%)
Changes in extraglomerular blood vessels	10 (62,5%)

Discussion

Complement activation and/or deposition is associated with both primary immune and nonimmune mediated forms of renal disease [9, 10]. Persistent proteinuria and tubulointerstitial lesions are important signs of progressive renal disease. When increased amounts of plasma proteins leak into the tubular lumen, complement is activated at the level of brush border with consequent tubulointerstitial damage, which can be decreased by inhibition of complement activation [11]. Activation of urinary complement proteins in situ by proximal tubular epithelial cells may contribute to the mediation of tubulointerstitial injury in patients with significant proteinuria, but the mechanism involved is unclear. [3,7,12-14].

According to some studies increased urinary levels of ammonia are present in patients with proteinuria, and it has been proposed that bicarbonate is protective against alternative-pathway-mediated damage to tubules by lowering the formation of ammonia and thus activation of the alternative pathway [15-17].

According to our data C3PTEC in kidney biopsies for one-year period is relatively low – 17,02%, but these deposits were considerably more frequent in patients with nephrotic than in patients with low to moderate range Pu. Such depositions were detected in 36,67% among patients with massive Pu and only in 7,8% among those with low to moderate range protein excretion.

The most common morphological finding in patients with C3PTEC was idiopathic nephrotic syndrome – minimal change disease and IgM nephropathy. The present data did not confirm results from some studies that such depositions were more frequently in membranous nephropathy, FSGS and membranoproliferative glomerulonephritis [18]. According to our data C3 PTEC were observed in 6% of patients with membranous glomerulonephritis and membranoproliferative glomerulopathy, and in 12,5% of patients with mesangioproliferative glomerulopathy.

We did not found such deposition in patients with FSGS. Among our patients 12,5% were with chronic interstitial nephritis. Other authors also confirmed such immune deposition in that renal pathology [19].

According to some investigators, intensity of complement cascade activation depends on the type of glomerular injury, the range of albuminuria and the range of kidney function deterioration [11,20]. Present data confirm these conclusions because mean Pu was 5,36 g/d and 68,75% from the patients had more than 3,5 g/d.

Serum creatinine in all patients was 197±120,21µmol/l, and creatinine clearance was 53,2±25,03ml/min/1.73m^2, so that all patients were classified from second to fourth stage of K/DOQI. Unlike some other studies, our present data did not confirm correlation between the intensity of C3 PTEC and serum creatinine and creatinine clearance [2,21,22].

Although relatively high frequency of C3 depositions in PTEC in nephrotic patients, we did not observed a correlation between such depositions and the degree of Pu. We established a correlation between protein excretion and duration of arterial hypertension before kidney biopsy.

The most common combination we observed was a nephrotic range Pu and renal insufficiency in 37,5% of patients.

Analised data from kidney biopsies of patients with C3 tubular depositions allow us to conclude that these deposits are commonest in patients with nephrotic range Pu in combination with elevated serum creatinine levels. Considerable part of patients biopsies had shown changes in glomerular mesangium in combination with significant tubulo-interstitial changes. At this stage of our study we are unable to exclude simultaneous effect of arterial hypertension duration, massive Pu and worsened renal function as a factors for C3 PTEC. Synthesis of C3 in renal tubules and its activation in renal interstitium is one of the most likely pathogenetical mechanism for progression of glomerulopathies with interstitial changes, which are of great importance for prognosis of the disease. C3 tubular deposits are frequently single-handed, but sometimes they are in combination with deposits of immunoglobulins. Among patients with nephrotic range Pu, C3 PTEC are found most frequently in minimal change disease and in mesangioproliferative IgM glomerulonephritis.

Probably C3 depositions in proximal tubular epithelia are due to complex pathologic mechanisms, but massive Pu, deterioration of renal function and duration of arterial hypertension are factors of great importance for C3 deposition. We conclude that C3PTEC are relatively rare findings in kidney biopsies, but probably they have a role for renal survival. Their incidence is higher in patients with massive Pu and in patients with minimal change disease and IgM nephropathy.

Conflict of interest statement. None declared.

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