Pediatr Nephrol (1999) 13:33–38

ORIGINAL ARTICLE

Yuji Inoue · Kazumoto Iijima · Hajime Nakamura
Norishige Yoshikawa

Two-year cyclosporin treatment in children with steroid-dependent nephrotic syndrome

Received: 4 March 1998 / Revised: 28 April 1998 / Accepted: 25 June 1998

Abstract We describe a prospective study of 2-year moderate-dose cyclosporin (CS) treatment in 13 children with steroid-dependent minimal change nephrotic syndrome (MCNS). CS treatment was commenced at 100–150 mg/m^2 per day after remission was attained with prednisolone therapy, was adjusted to a target trough level of 100 ng/ml, and was administered for 2 years. The number of relapses during CS treatment significantly decreased compared with before CS treatment, all patients were able to discontinue prednisolone therapy, and steroid toxicity was reduced; 54% of patients remained in remission during CS treatment. Renal biopsies performed before CS treatment all showed MCNS without tubulointerstitial lesions. Creatinine clearance and urinary β_2-microglobulin levels during CS treatment were normal in all patients, but renal biopsies performed after CS treatment revealed chronic CS nephrotoxicity in 7 patients. Clinical data, including CS dose and CS trough blood levels, were not significantly different between patients with and without nephrotoxicity. In conclusion, 2-year moderate-dose CS treatment in children with steroid-dependent MCNS is effective in preventing relapse and decreasing steroid toxicity. This treatment can, however, result in a high incidence of chronic nephrotoxicity. Renal function is not a reliable indicator of chronic CS nephrotoxicity. Renal biopsy is therefore necessary to monitor chronic CS nephrotoxicity.

Key words Chronic nephrotoxicity · Cyclosporin treatment · Minimal change nephrotic syndrome

Y. Inoue · K. Iijima · H. Nakamura
Department of Pediatrics, Kobe University School of Medicine, Kobe, Japan

N. Yoshikawa (✉)
Faculty of Health Science, Kobe University School of Medicine, Tomogaoka 7-10-2, Suma-Ku, Kobe, Japan 654
Tel.: +81-78-796-4515, Fax: +81-78-796-4509

Introduction

Children with minimal change nephrotic syndrome (MCNS) respond to corticosteroid therapy and have a benign long-term prognosis [1]. However, 40%–90% of responders have subsequent relapses [1–5], and children with steroid-dependent NS experience the serious side-effects that result from continuous steroid therapy. Cyclosporin (CS) is well recognized to be effective in the treatment of children with steroid-dependent NS [6–10]. We reported previously that 6-month moderate-dose CS treatment in children with steroid-dependent NS is effective in preventing relapses during CS treatment [11]. However, after the cessation of CS, NS recurred as frequently as before and most patients showed renewed steroid dependency. We also reported the effect of 12-month low-dose CS (75 mg/m^2 per day) treatment following 6-month moderate-dose CS treatment in children with steroid-dependent NS [12]. The number of relapses during 12-month low-dose CS (75 mg/m^2 per day) treatment was significantly decreased compared with before CS, but the relapse rate was higher on low-dose than moderate-dose CS treatment. Renal biopsies performed after 18 months of CS treatment showed no lesion that could be attributed to CS toxicity. In this study we report 2-year moderate-dose CS treatment of children with steroid-dependent NS. Repeat renal biopsies carried out after 2-year CS treatment showed chronic CS nephrotoxicity in half of these patients. We thus report the benefit and side-effects of 2-year moderate-dose CS treatment in children with steroid-dependent MCNS.

Patients and methods

The study was a prospective clinical trial that took place at Kobe University Hospital from 1991 to 1996. All patients and/or their parents gave their informed consent.

Patients

Patients were eligible for the study if they met the following criteria before being started on CS treatment: (1) they suffered from

steroid-dependent NS, (2) they experienced significant steroid toxicity, (3) they had had no treatment with cytotoxic agents within the preceding 6 months and had not received CS treatment, and (4) pre-CS biopsies showed MCNS without tubulointerstitial lesions. The definitions and criteria for NS, remission, and relapse were those used by the International Study of Kidney Disease in Children [13, 14]. NS was defined as urinary protein excretion ≥40 mg/m^2 per hour with hypoalbuminemia ≤25 g/l. Remission was defined as a reduction of urinary protein excretion to <4 mg/m^2 per hour (Albustix, 0 to trace) for 3 consecutive days. Relapse was defined as a reappearance of proteinuria ≥40 mg/m^2 per hour (Albustix, 2+ or greater) for 3 consecutive days. Steroid dependency was defined as a remission within 4 weeks of prednisolone therapy, with relapse occurring when the dose of prednisolone was reduced to below a critical level or within 2 weeks of discontinuation of therapy.

Steroid therapy

For steroid therapy, only prednisolone was used. The initial attack was treated with 2 mg/kg per day prednisolone, given in three divided doses (maximal dose 80 mg/day) for the first 4 weeks, followed by alternate-day prednisolone, with 1.3 mg/kg given as a single dose on the morning of every other day for 4 weeks (total 8 weeks). Relapses were treated with 2 mg/kg per day prednisolone given in three divided doses (maximal dose 80 mg/day) for the first 4 weeks, followed by alternate-day prednisolone at 2 mg/kg given as a single dose on the morning of every other day for 2 weeks, after which the dose was decreased by 0.5 mg/kg every 2 weeks (total 12 weeks).

CS treatment

CS (Sandimmun oral solution) treatment was started at a dose of 100–150 mg/m^2 per day given in two divided doses, after the patients had attained remission with prednisolone therapy. The dose of CS was adjusted to a target trough level of 100 ng/ml, as measured by monoclonal antibody fluorescence polarization immunoassay. CS was administered for 2 years without interruption, and then tapered off by 30 mg/m^2 per day every week. The protocol for prednisolone therapy during CS treatment was the same as described above. No medicine that might contribute to CS nephrotoxicity was given during CS treatment.

Patients were followed once a week for the first 4 weeks of CS treatment and monthly thereafter. At each follow-up visit the patients were asked about their symptoms and were monitored for any side-effects of CS treatment. The following tests and measurements were carried out at each visit: blood count (including hemoglobin, white blood cells, and platelets), serum creatinine, creatinine clearance, blood urea nitrogen, total cholesterol, total bilirubin, transaminases, alkaline phosphatase, serum uric acid, electrolytes, urinalysis, urinary β_2-microglobulin, blood pressure, body weight, and body height. Creatinine clearance was calculated by the method of Schwartz [15]. Hypertension was defined as diastolic pressure exceeding the upper normal limit (mean+2 SD). Renal biopsies were performed at the start and the end of CS treatment.

The standard deviation score for height and obesity were used to evaluate the degree of growth retardation and obesity in patients. The standard deviation score for height=(height – expected height at that age)/standard deviation for expected height at that age, while the obesity score=(weight – expected weight at that height)/expected weight at that height×100–100 (%).

Renal biopsy

Renal biopsies were performed by the percutaneous technique using a Tru-Cut needle under ultrasound control. All renal biopsy tissue samples were examined by light microscopy (following staining with hematoxylin-eosin, periodic acid-Schiff, and silver methenamine), immunofluorescence microscopy, and electron microscopy. Histological diagnosis of MCNS was based on the criteria of the International Study of Kidney Disease in Children [14, 16].

An investigator who was blinded to the treatment status reviewed pre- and post-CS treatment renal biopsies. The severity of chronic CS nephrotoxicity in post-CS renal biopsies was graded semiquantitatively on a scale from mild to severe: scattered area of tubulointerstitial lesions, mild; several areas of tubulointerstitial lesions, moderate; and extensive areas of tubulointerstitial lesions, severe [10].

Statistical analysis

The results were analyzed using StatView J-4.02 software [17]. The distribution of clinical variables between two groups was examined by Fisher's exact test. Continuous characteristics between two groups were compared with Wilcoxon rank-sum tests. Differences between study entry and study end were tested by Wilcoxon signed rank test. A two-tailed *P* value of less than 0.05 was taken to indicate significance. Results are presented as the mean±1 SD.

Results

Between May 1991 and April 1994, 13 children with steroid-dependent NS met the criteria for inclusion in the trial and were enrolled in the study. All patients completed the full trial. Renal biopsies performed 425±605 days before CS treatment showed that all patients had MCNS without tubulointerstitial lesions. Immunofluorescence microscopy of pre-CS renal biopsy samples showed slight diffuse mesangial deposition of IgM in 3 patients and slight diffuse mesangial deposition of C1q in 1 patient. Renal biopsies performed after CS treatment in 7 patients (group A) showed glomerular, tubulointerstitial and/or arteriolar changes, which have been attributed to CS toxicity (Fig. 1, Table 1). Tubulointerstitial lesions characterized by a combination of striped interstitial fibrosis and tubular atrophy were observed in all group A patients. Arteriolar lesions characterized by subendothelial widening with or without hyaline deposits were observed in 5 group A patients. Two patients showed scattered foci of tubulointerstitial lesions (mild), 4 showed several areas of tubulointerstitial lesions (moderate), and 2 showed extensive areas of tubulointerstitial lesions (se-

Table 1 Chronic nephrotoxicity in 7 patients after cyclosporin (CS) treatment (group A)

Patient no	Arteriolopathy	Striped interstitial fibrosis and tubular atrophy	Focal segmental and/or global glomerulosclerosis	Severeity
1	+	+	+	Severe
2	+	+	+	Moderate
3	+	+	+	Moderate
4	–	+	+	Moderate
5	–	+	–	Moderate
6	+	+	+	Mild
7	+	+	+	Mild

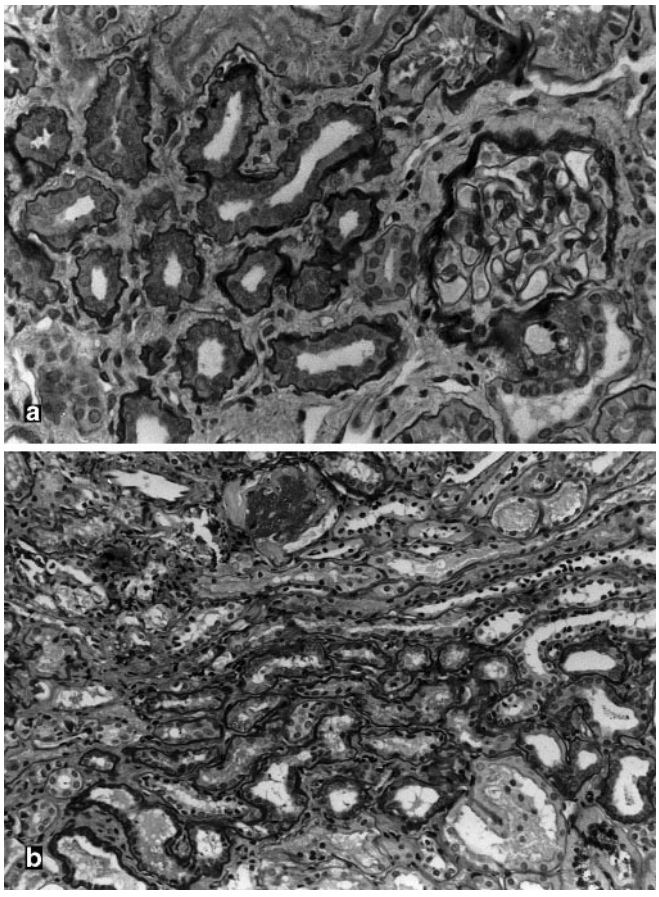

Fig. 1 Chronic cyclosporin nephrotoxicity; **a** arteriolopathy and tubular atrophy associated with interstitial fibrosis (periodic acid-Schiff, ×340); **b** focal and global glomerulosclerosis and striped tubular atrophy and interstitial fibrosis (periodic acid-Schiff, ×210)

vere). Renal biopsies performed after CS treatment in the other 6 patients (group B) still showed MCNS without tubulointerstitial lesions.

The clinical data obtained before CS treatment are summarized in Table 2. Sex ratio, age at onset, age at the time of study, duration of illness, number of relapses, and therapy before CS treatment were not significantly different between groups A and B. Cyclophosphamide therapy (2–3 mg/kg per day for 8–12 weeks) had been given previously in 6 group A and 3 group B patients.

The average number of relapses per patient during 6 months before CS treatment was 2.6±1.1 in group A and 1.8±1.2 in group B (Table 3). The number of relapses significantly decreased in both groups during 2-year CS treatment. Three patients in group A and 4 in group B experienced no relapse during CS treatment; 1 patient in group A and 2 in group B experienced one relapse and 3 patients in group A had more than two relapses. All patients required continuous prednisolone therapy during the 6 months prior to CS treatment. In contrast, all patients in groups A and B were able to discontinue prednisolone following CS treatment. The duration without prednisolone during CS treatment was 240–1,034 (576±254) days in group A and 564±717 (608±68) days in group B. The cumulative prednisolone dose during CS treatment was significantly reduced in both groups compared with before CS treatment. During 6 months after discontinuation of CS treatment, 2 of the 3 group A and 0 of the 4 group B patients without relapse during 2-year CS treatment maintained remission. NS relapsed in 5 group A and 6 group B patients within 6 months of discontinuation of CS treatment, with 5 group A and 3 group B patients reverting to their pre-CS treatment pattern, namely frequent relapses with steroid dependency.

CS doses, CS trough blood levels, creatinine clearance, and levels of serum creatinine, total cholesterol, and urinary β_2-microglobulin during CS treatment were not significantly different between groups A and B, with the exception of the CS dose at the 24th month (P=0.03) (Table 4). The mean standard deviation scores for height during 2-year CS treatment increased from −1.45±1.61 to −0.86±1.51 in the 13 patients (P=0.0046). The mean obesity scores during 2-year CS treatment decreased from 27.9%±24.9% to 1.2%±15.8% in the 13 patients (P=0.0046).

Hypertrichosis occured in 6 group A and 5 group B patients, and gingival hyperplasia occurred in 5 group A and 3 group B patients. Hypertrichosis and gingival hyperplasia became apparent 2–3 months after starting CS treatment, but were not severe enough to necessitate discontinuing CS treatment. Elevation of serum alkaline phosphatase to >500 U/l was observed in 6 group A and 4 group B patients. Transaminase levels were slightly elevated in 2 group A and 2 group B patients. Alkaline phosphatase and transaminase levels returned to normal after discontinuation of CS treatment. Hypertension oc-

Table 2 Clinical data before CS treatment[a]

	Group A	Group B
No. of patients	7	6
Sex ratio (M/F)	5/2 (1:0.4)	4/2 (1:0.5)
Age at onset (years)	5.5±4.0 (1.5–12.2)	7.9±4.5 (12.7–13.8)
Age at the time of study (years)	9.7±4.5 (4.1–14.4)	13.7±3.5 (8.4–16.8)
Duration of illness (years)	4.2±3.8 (1.7–11.8)	5.8±4.4 (1.8–13.7)
No. of relapses		
Total	10.3±4.9 (5–17)	11.0±5.2 (5–17)
6 months before CS	2.6±1.1 (1–4)	1.8±1.2 (1–4)
Therapy before CS (no. of patients)		
Steroid only	1	3
Steroid/cyclophosphamide	6	3

[a] Values represent mean±SD. Ranges are given in parentheses

Table 3 Effect of CS treatment[a]

	6 months before CS	During CS treatment			
		1–6 months	7–12 months	13–18 months	19–24 months
Group A					
No. of total relapses	18	3	1	5	4
No. of relapses per patient	2.6±1.1	0.4±0.8*	0.1±0.4*	0.7±0.8*	0.6±0.8*
Prednisolone dosage (mg/kg)	189±81	94±62*	9±14*	40±45*	24±29*
Group B					
No. of total relapses	11	1	0	1	0
No. of relapses per patient	1.8±1.2	0.2±0.4*	0*	0.2±0.4*	0*
Prednisolone dosage (mg/kg)	133±86	39±23*	7±17*	0*	0*

* $P<0.05$ compared with 6 months before CS
[a] Values represent mean±SD

Table 4 Laboratory data before and during CS treatment[a]

	Before treatment	6th month	12th month	18th month	24th month
Group A					
CS dose (mg/m^2 per day)		132±32	138±23	145±36	148±33*
Trough blood level (ng/ml)		95±31	100±33	89±32	116±30
Serum creatinine (mg/ml)	0.46±0.12	0.45±0.12	0.44±0.13	0.49±0.12	0.51±0.14
Creatinine clearance (ml/min per 1.73 m^2)	152±39	157±37	166±28	153±19	153±23
Serum total cholesterol (mg/dl)	183±30	182±34	177±27	174±31	174±32
Urinary β_2-microglobulin (μg/l)	166±166	187±158	79±31	129±57	78±42
Group B					
CS dose (mg/m^2 per day)		133±35	132±34	122±23	115±16*
Trough blood level (ng/ml)		112±22	105±42	134±53	115±32
Serum creatinine (mg/dl)	0.54±0.07	0.59±0.08	0.54±0.13	0.59±0.14	0.60±0.15
Creatinine clearance (ml/min per 1.73 m^2)	152±22	140±9	158±24	149±30	148±30
Serum total cholesterol (mg/dl)	184±31	183±32	180±30	177±24	174±23
Urinary β_2-microglobulin (μg/l)	109±84	48±20	72±56	45±33	56±17

* $P=0.03$
[a] Values represent mean±SD

curred during the first 2 weeks of CS administration in 1 group A and 1 group B patient. This was controlled by loop diuretics and calcium channel blockers. Tremor occurred in 1 group A and 1 group B patient. All side-effects associated with CS treatment disappeared after CS was discontinued or its dose reduced.

Discussion

Although about 95% of children with MCNS respond to corticosteroid therapy, 40%–90% of responders have subsequent relapses [1–5]. One of the major problems in the management of children who have frequent relapses is the serious side-effects resulting from continuous steroid therapy. Alkylating agents such as cyclophosphamide and chlorambucil have been used as adjuncts to steroids for inducing longer remission in frequently relapsing NS. The effect of these alkylating agents is well established in patients without steroid dependency, but they are unsatisfactory in steroid-dependent patients [18, 19]. Arbeitsgemeinschaft für Pädiatrische Nephrologie reported the effect of 12-week cyclophosphamide in steroid-dependent patients [20]. However, a number of investigators have reported the use of CS in children with steroid-dependent NS [6–10].

Although it is possible that a relapse may have precipitated entry into the study of otherwise stable patients, the number of relapses that occurred during 2-year CS treatment significantly decreased compared with during 6 months before CS treatment, and the cumulative prednisolone dose required during CS treatment was significantly reduced compared with during 6 months before CS treatment (Table 3). Of the 13 patients, 7 (54%) remained in remission during CS treatment. As a result, the degree of steroid toxicity, growth retardation, and obesity was reduced.

The beneficial effects of CS treatment were, however, accompanied by side-effects in all patients. Of greatest concern is chronic CS nephrotoxocity, characterized by tubulointerstitial lesions, focal glomerulosclerosis, and arteriolar lesions [21]. Chronic CS nephrotoxicity was present in 7 of the 13 patients, being severe in 1 patient, moderate in 4 patients, and mild in 2 patients. One should be wary, therefore, of the interpretation of tubulointerstitial lesions in patients with MCNS, since MCNS

is sometimes accompanied by focal tubular changes [14]. The same can be said for the interpretation of glomerulosclerosis in patients with idiopathic NS, since MCNS is sometimes accompanied by focal global glomerulosclerosis [14, 22, 23], and since the possibility of focal segmental glomerulosclerosis cannot be completeley excluded. In the present study, examination of pre-CS renal biopsy samples showed that tubulointerstitial lesions or glomerulosclerosis were absent in all patients. All patients responded to 4-week prendisolone therapy. In contrast, most patients with focal segmental glomerulosclerosis do not respond to steroid therapy. Arteriolar lesions, which have been considered the hallmark of CS nephrotoxicity [24–27], were present in 5 of these 7 patients. We therefore consider that the arteriolar, tubulointerstitial, and/or glomerular lesions observed on post-CS biopsy samples in our 7 patients were indicative of chronic CS nephrotoxicity, and these 7 patients had MCNS.

Many of the retrospective clinical reports concerning chronic CS nephrotoxicity in childhood NS are based on renal function. There are few pathological data concerning chronic CS nephrotoxicity in childhood NS [10, 28]. This study is unique because it was prospective and all patients had pre- and post-CS biopsies. Habib and Niaudet [28] demonstrated moderate or severe tubulointerstitial lesions after 4–63 months of CS treatment in 21 of 37 children with MCNS. Multivariate analysis of renal biopsy samples from CS-treated patients with autoimmune disease has shown that high initial dose, male gender, and episodes of acute renal dysfunction are major risk factors for the chronic pathological manifestations of CS nephrotoxicity [29]. In our patients with chronic CS nephrotoxicity, CS dosage was about 150 mg/m^2 per day, trough blood levels were about 100 ng/ml, and creatinine clearance and urinary β_2-microglobulin levels during CS treatment were normal. CS doses, CS trough levels, and serum total cholesterol levels were not significantly different between patients with nephrotoxicity (group A) and patients without nephrotoxicity (group B), with the exception of the CS dose at the 24th month. Although there was no statistical significance due to the small number of patients, the number of relapses during 6 months before CS treatment and during CS treatment was higher and the age at the start of CS treatment was younger in group A patients. Young age at the start of CS treatment and high number of relapses during CS treatment may be risk factors for chronic CS nephrotoxicity in children with steroid-dependent NS. Since the CS dose was not increased in patients who relapsed, it is possible that patients with proteinuria may be more susceptible to chronic CS nephrotoxicity.

In a previous study, we treated 19 children with steroid-dependent NS with 6-month moderate-dose CS, followed by 12-month low-dose CS (75 mg/m^2 per day) (total 18 months) [12]. The cumulative remission rate at 18 months after the start of CS treatment was 37% in the previous 18-month CS treatment and 54% in the current 2-year CS treatment. Post-CS treatment biopsy samples revealed that none of the patients treated with the 18-month CS exhibited chronic CS nephrotoxicity, compared with 58% of the patients treated with the current 2-year CS. Because of a high incidence of chronic nephrotoxicity, we cannot recommend this 2-year moderate-dose CS treatment for children with steroid-dependent NS. A prospective trial is currently in progress to evaluate the benefits and chronic CS nephrotoxicity of 6-month moderate-dose CS, followed by 18-month low-dose CS (75 mg/m^2 per day) (total 2 years).

In conclusion, 2-year moderate-dose CS treatment in children with steroid-dependent MCNS can be effective in preventing relapse and decreasing steroid toxicity, but can result in a high incidence of chronic nephrotoxicity. Renal function is not a reliable indicator of chronic CS nephrotoxicity. Renal biopsy is therefore necessary to monitor chronic CS nephrotoxicity within 2 years of the start of CS treatment.

Acknowledgements The authors thank Fumihiko Suehiro, Souichi Kodama, Takashi Sakurai, Shinichirou Uehara, Kouichi Nakanishi, and Kukiko Noguchi for their excellent support in collecting data.

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LITERATURE ABSTRACT

J. Bariety · D. Nochy · C. Mandet · C. Jacquot · D. Glotz
A. Meyrier

Podocytes undergo phenotypic changes and express macrophagic-associated markers in idiopathic collapsing glomerulopathy

Kidney Int (1998) 53:918–925

Collapsing glomerulopathy (CG), a severe form of focal segmental glomerulosclerosis (FSG), is characterized by tuft retraction and consolidation in numerous glomeruli and changes in podocyte morphology and topography. Other glomeruli are less affected. Collapsing glomerulopathy is also characterized by tubulointerstitial atrophy and fibrosis. The pathophysiology of the glomerular and tubulointerstitial lesions is poorly understood. We studied renal tissue of five Black and three White patients, all human immuno-deficiency virus (HIV) negative, with nephrotic syndrome, renal failure, and histological evidence of CG. Immunohistochemistry identified normal podocyte phenotypes by podocalyxin, vimentin and complement receptor 1 (CR1) labeling. Three monoclonal antibodies were used to further characterize podocyte epitopes: anti-CD68 clone KP1, anti-CD68 clone PG-M1 and anti-M130 clone M18 (Ber-MAC3). Light microscopy of collapsed glomeruli showed podocyte swelling, vacuolization, multinucleation, ''cobblestone-like'' alignment around the glomerular tuft, and pseudo-crescent formation in Bowman's space. In collapsed glomeruli, podocalyxin, vimentin and CR1 labeling tagged both normal and vacuolated podocytes still attached to the GBM, but labeling was not found in cobblestone-like podocytes or in podocytes detached from the GBM. Conversely, numerous podocytes undergoing detachment and shedding into Bowman's space expressed macrophagic-associated epitopes. Cells with macrophagic-associated epitopes clumped in cystically dilated tubules and were aligned in tubules of smaller caliber. Their appearance was that of viable cells. There was no morphologic indication that these cells expressing macrophage-associated antigens originated from outside the glomeruli or outside the tubules. We conclude that in CG podocytes detach from the GBM, lose their normal podocytic phenotype and acquire macrophage differentiation antigens. The presence of cells with such antigens in tubular lumens suggests that detached metaplastic podocytes progress along the tubule or, alternatively, that CG tubular cells also undergo metaplastic changes into macrophage-like cells.