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A Case of Nephrotic Syndrome with Nephrotoxicity Induced by Low-Dose Cyclosporin Treatment

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We report a 3-year-old girl with steroid resistant nephrotic syndrome (NS) who developed nephrotoxicity by low-dose cyclosporin (CsA) treatment. Initial prednisolone (PSL) treatment and subsequent additional cyclophosphamide treatment were not successful in leading her into remission. The first renal biopsy finding revealed neither a glomerular nor interstitial change. CsA therapy was initiated in addition to ongoing glucocorticoid therapy at 6 months from the time of onset. Proteinuria disappeared 3 weeks later and the patient went into complete remission. After experiencing the first relapse, the patient was gradually weaned from CsA, and treatment continued with 30 to 50 ng/mL of trough concentration. No elevations of the serum creatinine, serum urea, serum potassium, excretion of urinary β_2-microglobulin, or urinary *N*-acetyl-β-D-glucosaminidase were demonstrated in the follow-up. A second renal biopsy specimen obtained 1 year later showed a tubulo-interstitial change, containing tubular atrophy and interstitial fibrosis, both of which are consistent with the morphological change associated with CsA nephrotoxicity. A follow-up biopsy should be done in order to evaluate the CsA nephrotoxicity, regardless of the treatment dosage.

Key words: cyclosporin; nephrotic syndrome; nephrotoxicity

Cyclosporin (CsA) is a very effective immunosuppressive agent that has been used in the treatment of steroid dependent or resistant nephrotic syndrome (NS) (Meyrier et al., 1991; Niaudet et al., 1991; Niaudet, 1992). However, CsA may have adverse effects upon the kidneys, and long-term treatment is associated with irreversible renal damage consisting of focal glomerular sclerosis and interstitial nephritis (Mihatsch et al., 1994). Nephrotoxicity has occurred in patients following high doses of CsA, and the likelihood of its occurrence depends on the trough concentration level of the drug (Collaborative Study Group of Sandimmun in Nephrotic Syndrome, 1991). In this paper we describe a case of a NS patient suffering from CsA nephrotoxicity though she was treated with a low blood concentration.

Abbreviations: CsA, cyclosporin; NS, nephrotic syndrome; PSL, prednisolone

Patient Report

In September 1996, a 3-year-old girl was referred to us from a satellite hospital with symptoms of NS consisting of massive proteinuria, edema and oliguria, which had begun 4 months earlier. She had been treated by prednisolone (PSL) and subsequent additional cyclophosphamide treatment but the disease was not resolved by means of these agents. At the time of admission to our hospital, she retained symptoms of NS—anasarca, ascites, oliguria (150 to 250 mL/24 h) and hypertension (from 58 to 112 mmHg). Laboratory findings revealed hypoproteinemia (serum total protein: 4.6 g/dL, serum albumin: 2.3 g/dL) and hypercholesterolemia (serum total cholesterol: 479 mg/dL), though the serum urea level (8 mg/dL) and serum creatinine level (0.2 mg/dL) were nor-

mal. Urinalysis showed massive proteinuria (over 600 mg/dL concentration in the morning urine and 4.2 g/24 h in urinary protein excretion), but hematuria and abnormal urinary sediment were not shown (Table 1). On September 25, a needle renal biopsy was performed from the lower pole of the right kidney. In the renal biopsy specimen, which contained 8 glomeruli, only 1 glomerulus showed global sclerosis; the other glomeruli and tubulointerstitia did not show any morphological change (Fig. 1). Any depositions of immunoglobulins and components, which were examined by immunofluorescent study, were not observed in the glomeruli. Beginning on October 21, CsA was administered at a 50 mg/day (3.5 mg/kg/day) initial dose in addition to the ongoing PSL treatment. Blood concentration of the drug was measured regularly twice a week by fluorescence polarization immunoassay method using monoclonal antibody, and was maintained in a range of 60 to 90 ng/mL, and never exceeded 100 ng/mL during the entire period of treatment (Fig. 2). Three weeks after CsA treatment began, proteinuria appeared to be minimizing and had completely dis-

Table 1. Laboratory data on admission

White blood cell	(/μL)	12,000
Red blood cell	(/μL)	455×10^4
Hemoglobin	(g/dL)	13.3
Hematocrit	(%)	39.3
Platelet	(/μL)	37.3×10^4
Na	(mmol/L)	138
K	(mmol/L)	4.0
Cl	(mmol/L)	100
Blood urea nitrogen	(mg/dL)	8
Cr	(mg/dL)	0.2
Urea acid	(mg/dL)	4.2
Ca	(mg/dL)	8.6
P	(mg/dL)	3.7
Serum total protein	(g/dL)	4.6
Serum albumin	(g/dL)	2.3
Total cholesterol	(mg/dL)	479
Urinalysis		
pH		7.0
Protein	(mg/dL)	600 (4.2 g/day)
Glucose	Negative	
Occult blood	Negative	
Sediment		
Red blood cell	(/hpf)	1–4
White blood cell	(/hpf)	5–9
U-β_2MG	(μg/L)	94
U-NAG	(IU/L)	8.0

hpf, high power field; U-β_2MG, urinary β_2 microglobulin; U-NAG, urinary *N*-acethyl-β-glucoseaminidas.

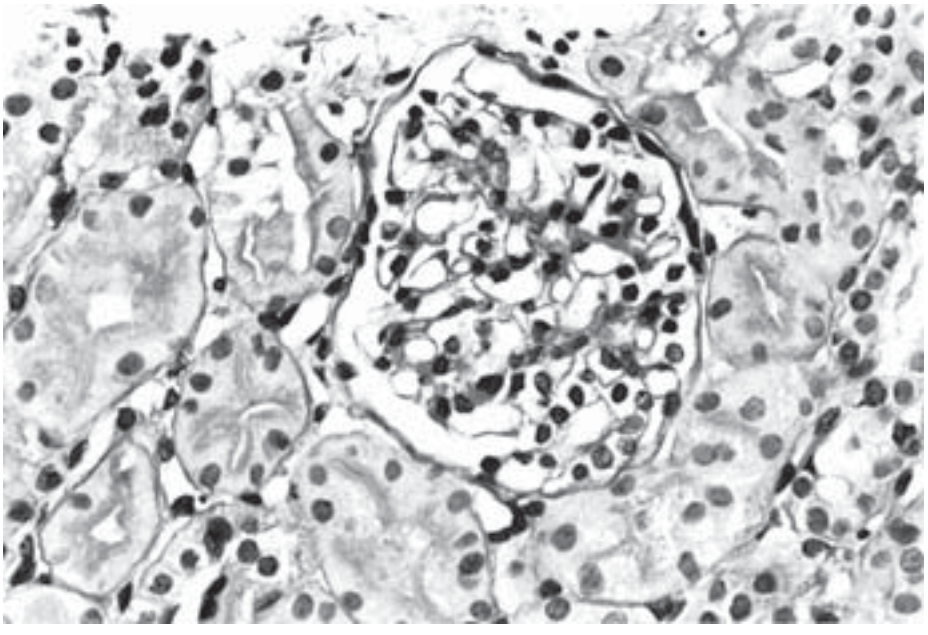

Fig. 1. Light micrograph of first renal biopsy specimens showing normal tubulointerstitia and glomerulus (periodic acid-Schiff stain × 200).

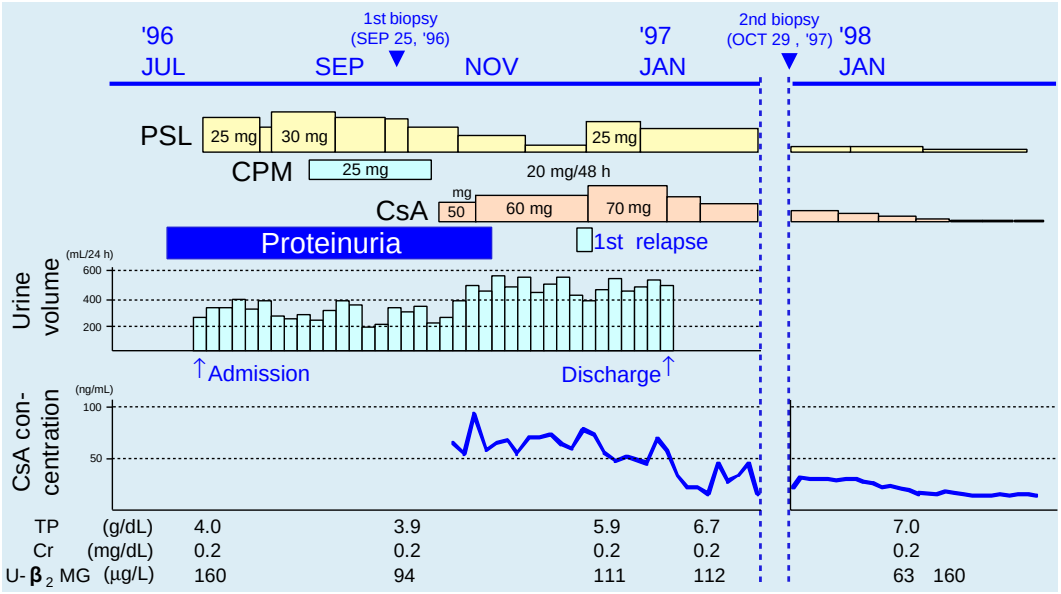

Fig. 2. Clinical course of the present patient. PSL, prednisolone; CPM, cyclophosphamide; CsA, cyclosporin; TP, serum total protein; Cr, serum creatinine; U-β_2 MG, urinary β_2-microglobulin.

appeared 1 month following administration. On December 19, when the PSL dose was reduced to 20 mg/48 h every other day, the patient relapsed with no apparent cause. After the PSL dose was temporarily raised, the relapse was resolved, and the patient was discharged on February 24, 1997. CsA was tapered, and treatment was continued in a range of 30 to 50 ng/mL of whole blood concentration. The CsA dose ranged from 1 mg/kg/day to 1.5 mg/kg/day during the follow-up period. PSL was simultaneously continued in combination with a small amount of CsA. Blood and urinary analyses were performed regularly. No elevation of the serum creatinine, urea, and potassium levels and excretion of urinary β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase were demonstrated during the follow-up period. In order to evaluate the subsequent renal morphological change, a second renal biopsy was performed 1 year later on October 29, 1997. Eighteen glomeruli were obtained, 17 of which showed mild or moderate mesangial cell proliferation, though neither segmental lesion nor global sclerosis was seen (Fig. 3A). Morphological changes were unexpectedly found in the tubulointerstitia, which is regarded as a feature of CsA nephrotoxicity. Tubular atrophy and interstitial fibrosis were seen focally in some fields by light microscopy (Fig. 3B). Vacuolization in tubular epithelial cells was not identified. No elevation of the serum creatinine (0.2 mg/dL), serum urea (14 mg/dL), or excretion of urinary β_2-microglobulin (63 μg/L) was demonstrated at the time of the second biopsy. In consideration of the above histological findings, CsA treatment was discontinued in July, 1998.

Discussion

Our patient suffered from nephrotoxicity within the 1st year of CsA administration, although she had been treated with a low-dose treatment. The CsA dose was reduced within the first 2 months, and continued at 30 to 50 ng/mL of trough concentration during almost all of the treatment period. CsA nephrotoxicity is characterized as hyalinization of afferent arteries, tubular atrophy and stripped interstitial fibrosis (Bergstein, 1992); tubular atrophy and stripped interstitial fibrosis were seen in the present patient. The mesangial proliferation in the present patient is not considered to be a morphological

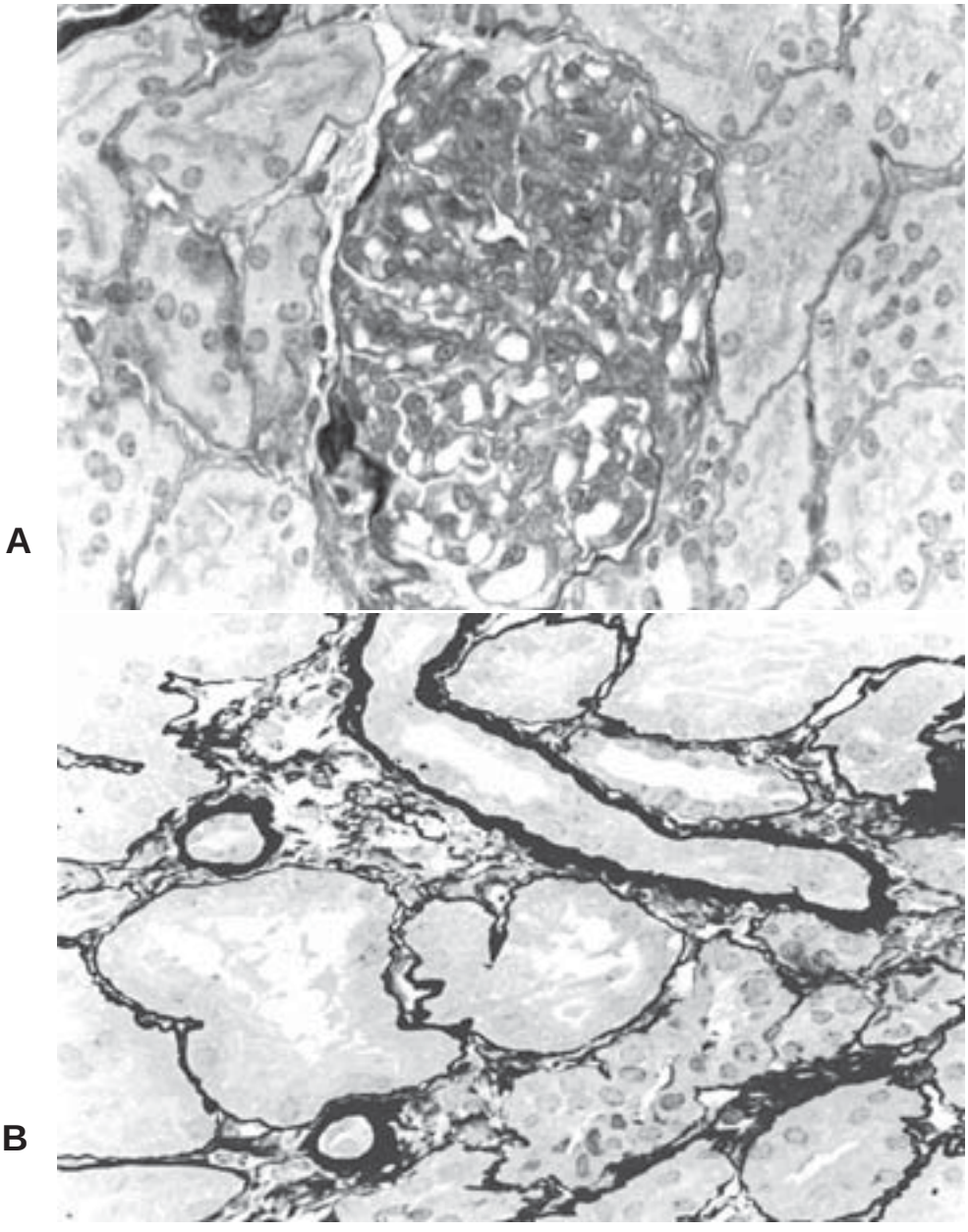

Fig. 3. Light micrographs of second renal biopsy specimens showing mesangial proliferation (**A**: periodicacid-Schiff stain × 400), stripped interstitial fibrosis and tubular atrophy (**B**: PAM × 400).

change indicative of CsA nephrotoxicity, but as a glomerular change seen in cases of diffuse mesangial hypercellularity, which was addressed by the International Study of Kidney Disease in Children (1981).

It has been considered that the deterioration of renal function depends on the trough concentration level of the treatment drug, and that long-term use of CsA results in chronic renal injury, which is not corroborated by biochemical

laboratory findings (Collaborative Study Group of Sandimmun in Nephrotic Syndrome, 1991; Tanaka et al., 1993). In previous literature authored by Yoshikawa and colleagues (1995), 7 of 13 patients with steroid-dependent NS, managed with 100 ng/mL of whole blood level for 2 years, suffered subsequent chronic nephrotoxicity, although none of these patients demonstrated elevation of both serum creatinine and urinary β_2-microglobulin during the administration period. Other published reports concerning a moderate dose of CsA treatment showed a relatively high incidence of morphological change. The reported incidence of nephrotoxicity among patients with NS ranges from 25 to 63% (Brodehl et al., 1988; Niaudet et al., 1988; Sieberth et al., 1992). Conversely, a publication by Gregory and colleagues (1996) describing long-term use has drawn attention to a relatively low incidence; the authors showed that the incidence of nephrotoxicity in biopsy specimens obtained after 12 to 41 months of therapy is 17%.

Based on reported studies, the incidence of nephrotoxicity in patients with steroid resistant nephrotic syndrome is higher than that in patients with steroid dependent nephrotic syndrome: 22 to 66% versus 0 to 10% (Capodicasa et al., 1986; Niaudet et al., 1988, 1991; Neuhaus et al,. 1992). However , steroid resistant nephrotic syndrome itself carries a substantial risk of chronic renal insufficiency and end-stage renal disease (Mampaso et al., 1981). Other studies showed that the risk of CsA nephrotoxicity was associated with increased patient age, preexisting deteriorating renal function, hypertension and decreased renal blood perfusion (Thiel et al., 1986; Feutren et al., 1992). We found no evidence, however, to explain why our patient suffered CsA nephrotoxicity in response to a relatively small dose. We speculate that the condition of the patient's illness at the time of commencement of CsA treatment may relate to a increased risk for nephrotoxicity. When CsA was initiated, she still had symptoms of NS including massive proteinuria, edema, hypertension and oliguria, suggesting the existence of poor renal blood perfusion and decreased renal function which were not associated with detectable laboratory data. To our knowledge, preexisting renal dysfunction is one of the high risk factors of increased CsA nephrotoxicity. In previous studies using ischemic rat kidneys, poor renal blood perfusion has proven to be one of the increasing risk factors (Jablonski et al., 1986; Thiel et al., 1986). We consider that CsA administration on the hypoperfusion kidney in the initial presentation might increase CsA intoxication, and result in subsequent tubulointerstitial change. Accordingly, regardless of the proceeding CsA dose, a careful follow-up, including re-evaluation of histological changes by second renal biopsy, is warranted in this patient.

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