

Clq nephropathy in a 2-year-old boy presenting with steroid resistant nephrotic syndrome

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(Received June 13, 2007; Accepted July 27, 2007)

We experienced a case of a 2-year-old boy, who presented with steroid resistant nephrotic syndrome, which developed insidiously. Renal biopsy revealed that he had focal and segmental glomerulosclerosis on light microscopy, dominant mesangial deposition of Clq by immunofluorescent staining, and electron dense deposits on electron microscopy, which are all compatible with Clq nephropathy. He had no clinical sign of any collagen diseases, including systemic lupus erythematoses. So, the diagnosis of Clq nephropathy was made. An intensive treatment by a combination of cyclosporine, prednisolone and methylprednisolone pulse therapy was successful in achieving remission and disappearance of proteinuria in this patient. Although he developed hypertension requiring calcium blocker and angiotensin converting enzyme inhibitor, his renal function stayed within normal limit for 3 years after the initiation of the treatment. The growth was well preserved during the 3 years of treatment with almost unchanged SD scores for height. He has delay in speech, which may not be associated with the etiology of his nephropathy, based on the absence of such association in the previous reports. Clq nephropathy is still a controversial clinical entity, so accumulation of the cases may help further understand the pathogenesis and clinical manifestation of Clq nephropathy.

Key words: steroid resistant nephrotic syndrome, focal segmental glomerulosclerosis, Clq nephropathy, methylprednisolone pulse therapy, cyclosporine

INTRODUCTION

Predominant deposition of Clq in the glomerular mesangium is frequently documented in the cases with systemic lupus erythematoses (SLE). However, in some patients without any clinical and serological evidence of SLE, Clq deposition is recognized along with concomitant presence of electron dense deposit on electron microscopy, suggesting of a new clinical entity, named Clq nephropathy [1, 2]. The clinical course of Clq nephropathy varies from asymptomatic urine abnormality to steroid resistant nephrotic syndrome, leading to some controversy on the significance of Clq nephropathy as a distinct clinical entity. Although clinicopathologic information about Clq nephropathy is now getting accumulated, it is not yet fully understood. Accumulation of case reports of Clq nephropathy may contribute to our further understanding of Clq nephropathy. We experienced a case of a 2-year-old boy, who presented with steroid resistant nephrotic syndrome, and whose histological findings were compatible with Clq nephropathy, followed by remission by a combination treatment of cyclosporine, prednisolone and methylprednisolone pulse therapy.

CASE REPORT

A 2-year and 7 month-old boy was admitted to Hiratsuka City Hospital because of the persistent edema on face, eye lids, and extremities lasting for more than 10 days. Family history was negative for kidney diseases, hearing loss, and collagen diseases. Past history revealed normal delivery at full term without asphyxia. He had a mild developmental delay, especially in speech. He could not address a meaningful word, although he could understand and follow his parent's orders at the age of 2 years and 7 months. During the 6 months prior to the admission, his mother had noticed several episodes of transient eye lid edema lasting for several days followed by spontaneous regression once or twice in a month.

Physical examination on admission was unremarkable except for moderate edema on bilateral eye lids and lower extremities. Blood pressure was 83/36 mmHg. He was active and well nourished. His height was 87cm (-0.88 SD), and weight as 13.3kg. No episodes of facial erythema, stomatitis, and arthritis were noted.

Laboratory findings revealed that he had marked hypoalbuminemia (1.6 g/dL) with heavy protein-

uria (1970 mg/dL, or 14.1 mg/mg creatinine) and microscopic hematuria (3+). Hyperlipidemia (T-Chol 805 mg/dL, TG 445 mg/dL) was also noted. Serum complements were normal (C3 122 mg/dL, C4 26 mg/dL), and anti-nuclear antibody was negative (<40). Renal function was intact (Creatinine 0.19 mg/dL, BUN 7 mg/dL). HBs antigen, HCV antibody, PR3-ANCA, and MPO-ANCA were all negative. There was no evidence of streptococcal infection.

Based on his clinical and laboratory findings, he was diagnosed as having nephrotic syndrome, and oral prednisolone of 30 mg/day was initiated. Hematuria disappeared in a week, and the edema gradually decreased over a couple of weeks after the initiation of steroid therapy. However, heavy proteinuria persisted without elevation of serum albumin level. At the end of prednisolone administration for 4 weeks, urinary protein/creatinine ratio (mg/mg) was 16.0, and serum albumin was 1.7 g/dL, suggesting that his nephrotic syndrome was resistant to the ordinary steroid treatment. We then obtained renal specimen by needle biopsy with informed consent by his parents.

Histological findings are shown in Fig. 1. Fifteen glomeruli were observed under light microscopy, and 13 out of them showed minor glomerular abnormalities. However, segmental sclerosis was noted in the remaining 2 glomeruli observed (Fig. 1a, b, c). Spike formation or stippling of the glomerular basement membrane was absent in PAM staining. There was

no obvious mesangial deposit in Azan staining. Immunofluorescence study revealed predominant mesangial Clq deposition (Fig. 1d). IgA and IgM were also demonstrated, although with much less intensity than that of Clq. C3 and fibrinogen was absent in immunofluorescence study. Mesangial electron-dense deposits were found by electron microscopy. Based on these histological findings, the diagnosis of Clq nephropathy with focal segmental glomerulosclerosis was made.

The histological diagnosis of focal segmental glomerulosclerosis prompted us to start methylprednisolone pulse therapy along with oral administration of cyclosporine and prednisolone. Methylprednisolone was administered intravenously in the doses of 30 mg/kg/dose on 3 consecutive days. A set of three-day-course of methylprednisolone was repeated in a total of 5 times, at 1, 4, 8, 12 weeks after the initial course. Cyclosporine (Neoral®) of 100 mg/day was administered for 12 weeks, then tapered to 80 mg/day. The trough levels of cyclosporine were 130 to 140 ng/mL during the first 12 weeks, and 80 to 100 ng/mL after the 13th week. Prednisolone was administered in a dose of 12 mg every day for 4 weeks, and then tapered to 12 mg on alternate days.

Proteinuria was gradually decreased around 5 weeks after the initiation of above mentioned combination therapy. Urine protein/creatinine ratio (mg/mg creatinine) fell down to 2.1 in 6 months, while serum

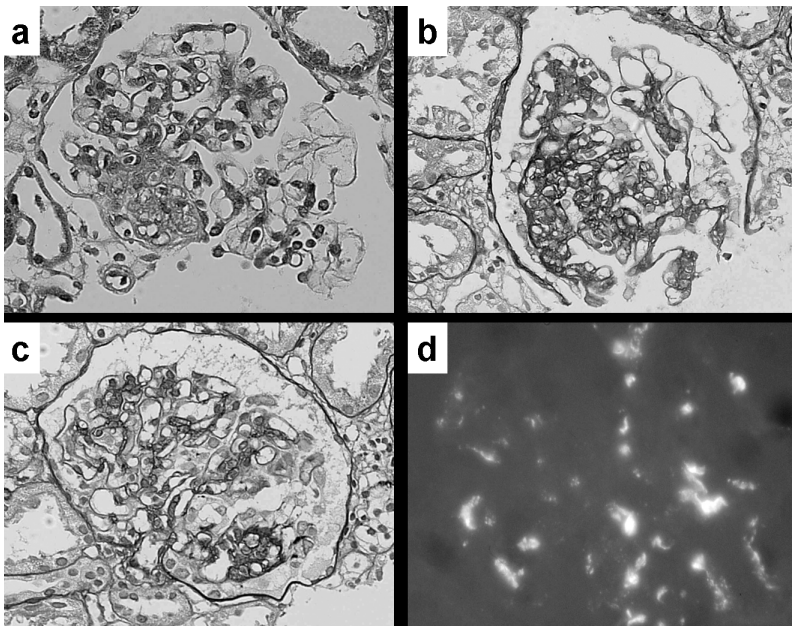


Fig. 1 Focal and segmental sclerosis on light microscopy (PAS stain in Fig. 1a, PAM stain in Fig. 1b, c; original magnification $\times 400$) and immunohistochemical demonstration of Clq deposition in a glomerulus (Fig. 1d).

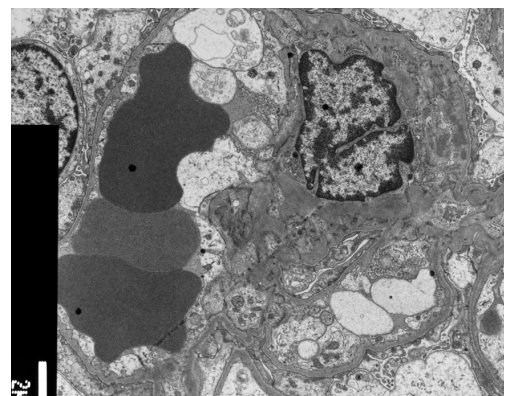


Fig. 2 Electron dense deposits were demonstrated in the mesangium by electron microscopy.

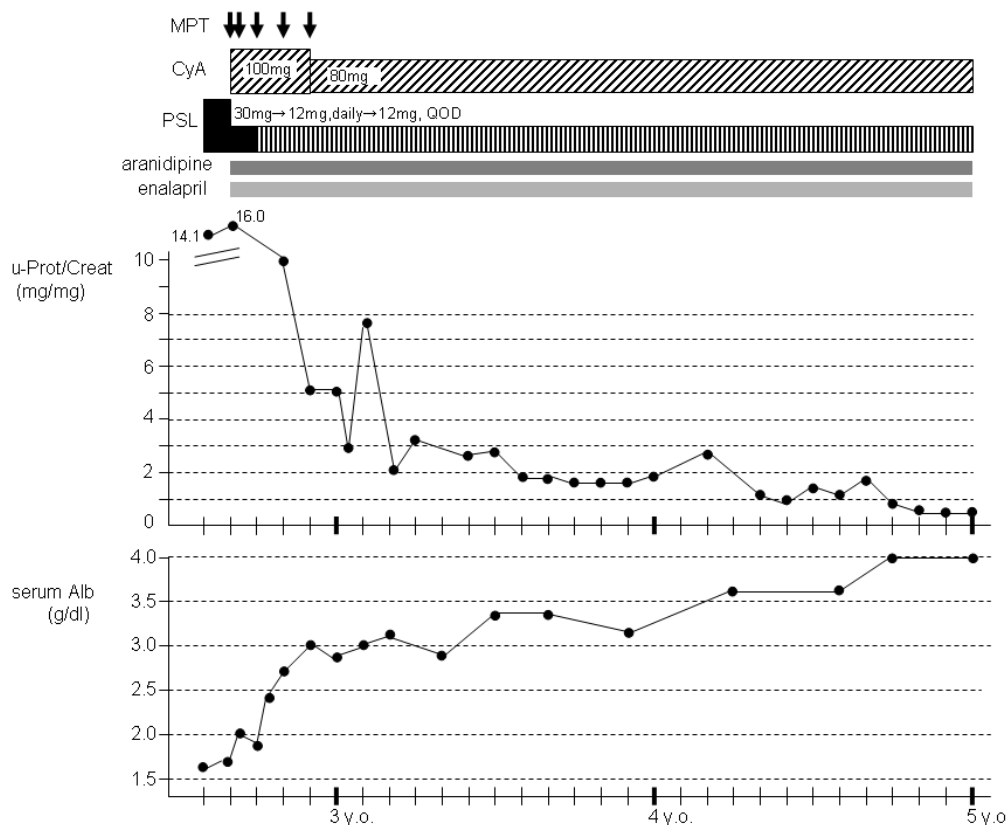


Fig. 3 Clinical course of the patient.

albumin rose up to around 3.0 g/dL in 3 months. Blood pressure was elevated to 120/60 mmHg during the initial prednisolone treatment of 30 mg/day before the renal biopsy, and further elevated up to 136/72 mmHg after the introduction of the combination treatment of mPSL pulse and cyclosporine. Calcium antagonist (aranidipine, 2 mg/day) and ACE inhibitor (enalapril, 1.25 mg/day) were then administered, and the hypertension was well controlled. Renal function stayed normal (Creatinine 0.49 mg/dL) at the age of 5 years and 6 months, 34 months after the introduction of the combination therapy. Hypertrichosis and gingival hyperplasia related to cyclosporine treatment were noted, although they were mild in severity. His height at the age of 5 years and 5 months was 105.5 cm (-0.93 SD). Growth velocity during the treatment has been rather well preserved. Urinalysis at the age of 5 years showed almost normal values for proteinuria and hematuria. He is able to address only a few meaningful words, but he can understand what the other people say, and has no delay in motor development.

DISCUSSION

Clq nephropathy was first reported by Jones and Magil [3] in 1982. Jennette and Hipp [1, 2] proposed to define the clinical entity as Clq nephropathy by the following criteria: (1) the presence of predominant or codominant deposition of Clq in the mesangium on immunofluorescence, (2) corresponding mesangial or paramesangial electron-dense deposits under electron microscopy, and (3) lack of clinical and pathological evidence of systemic lupus erythematoses. The case presented here was compatible with all of the above

criteria. A variety of histological findings by light microscopy have been reported, including minor glomerular abnormalities, mesangial proliferative glomerulonephritis with or without segmental sclerosis, and focal segmental glomerulosclerosis (FSGS). Membranoproliferative glomerulonephritis and membranous nephropathy were also reported, although infrequently. FSGS was noted in our case presented. The frequency of FSGS in Clq nephropathy varies in several reports [4, 5, 6, 7], from 7% [6] (2 out of 30 cases) to 89% [5] (17 out of 19 cases). FSGS was not included in the series reported by Jennette and Hipp [1]. The difference may come from the different criteria as to when renal biopsy is indicated in different countries. The report from Japan by Fukuma [6] *et al.* revealed FSGS in 2 out of 30 cases (7%). Both of the 2 cases, one with asymptomatic proteinuria and the other with nephrotic range proteinuria, progressed to endstage renal failure in 10 to 15 years. Lau [8] *et al.* reported that the patients with Clq nephropathy presenting with nephrotic syndrome have rather poor prognosis as half of those progress to endstage renal failure in 3 years. Although the present case responded to a combination treatment with oral prednisolone, cyclosporine, and intravenous methylprednisolone pulse therapy, and his renal function is stable 3 years after the initiation of treatment, we should be very careful as to the long-term prognosis in terms of renal function. However, aggressive treatment by a combination of cyclosporine, prednisolone and methylprednisolone pulse therapy could be a treatment of choice for Clq nephropathy with FSGS. Methylprednisolone pulse therapy has been shown to be effective in steroid resis-

tant nephrotic syndrome [9, 10]. Cyclosporine has been also demonstrated to be effective in treating steroid resistant nephrotic syndrome [11, 12].

The mode of onset in the present case is interesting in that the patient developed nephrotic symptoms insidiously, and that multiple episodes of spontaneous amelioration of lid edema were repeatedly recognized during the six months prior to admission. If urinalysis was performed during this six month-period, the patient could have been diagnosed as Clq nephropathy presenting with asymptomatic proteinuria, then progressed to nephrotic syndrome. Nishida *et al* [13] reported spontaneous improvement of Clq nephropathy without steroid treatment in a patient, who had mild proteinuria with microscopic hematuria, and histological findings compatible with membranoproliferative glomerulonephritis. Spontaneous remission was also reported by Davenport *et al* [14]. It is noteworthy that the severity of proteinuria of our patient might be fluctuating at least at an early stage of the disease with a tendency of spontaneous, but transient improvement.

It is uncertain whether the delay in speech ability in the present case has something to do with Clq nephropathy. The association or co-existence of other diseases with Clq nephropathy has been reported. Hanevold *et al.* reported a case of Clq nephropathy associated with Gitelman syndrome [15]. Roberti *et al.* reported a case of Clq nephropathy in a child with chromosome 13 deletion and retinoblastoma [16]. Although chromosomal analysis was not performed in our patient presented, he had no past history of retinoblastoma, suggesting that the genomic background including abnormality of chromosome 13 might be absent. The external phenotype of our patient is devoid of any anomalous features including so-called minor anomalies, suggesting that he does not have large chromosomal defects. Also he has normokalemia and no acid-base disturbances such as Gitelman syndrome. So far, there is no report on the association of Clq nephropathy and delay in speech or autism, so, at present, we think that the association is just a coincidental event. Further accumulation of cases with Clq nephropathy in association with some neurological abnormalities, including delay in speech or autism, will help us understand the relationship between Clq nephropathy and neurological/behavioral dysfunction.

Whether Clq nephropathy is an early manifestation of SLE or not is an interesting issue. Previous reports, when Clq nephropathy was not recognized, deal with late onset SLE in patients with idiopathic glomerulonephritis [17, 18]. Some cases had positive glomerular Clq deposition along with other complements and immunoglobulins, although the predominance of Clq deposition was not described. The extrarenal manifestations or positive serological findings for SLE developed 1 to 10 years after the onset of nephropathy. So, we should be carefully watching for the delayed onset of SLE also in our patient. At least during the 3 years of observation, he was devoid of any clinical and serological evidence of SLE. Recently, Sharman *et al* [19] proposed that the term "Clq nephropathy" is preferable to "seronegative lupus nephritis", because delayed development of SLE in patients with Clq nephropathy is rather rare.

In summary, we experienced a 2-year-old boy with Clq nephropathy who presented with insidious onset of nephrotic syndrome, which was resistant to oral administration of steroid alone, but responded to a combination treatment of prednisolone, cyclosporine and methylprednisolone pulse therapy. The patient is in remission and the renal function is stable 3 years after the initiation of the treatment, although long-term observation is crucial.

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