

Case Report

C1q Nephropathy in a 2-Year-Old Boy: A Case Report

Reika Omura, Hiroshi Tamura*, Keishiro Furuie, Shohei Kuraoka, Hitoshi Nakazato

Department of Pediatrics, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Email address:

bohm1905HT@kuh.kumamoto-u.ac.jp (Hiroshi Tamura)

*Corresponding author

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Abstract: *Background:* C1q nephropathy occurs when C1q is significantly deposited in the mesangial region and systemic lupus erythematosus can be excluded as a diagnosis. *Clinical Description:* A case of a 2-year-old boy who was diagnosed with steroid-resistant C1q nephropathy. As he was initially managed as a case of idiopathic nephrotic syndrome, prednisolone was administered. However, as his condition did not improve with steroid treatment, other causes for nephrotic were considered, including infections. As it was initially refractory to steroid treatment, a cytomegalovirus infection was strongly considered. Based on the histological findings, C1q deposition was noted in the mesangium, which confirmed the diagnosis of C1q nephropathy. Cyclosporine A was initiated, which resulted in complete remission from the disease. When administering high doses of steroids, it is necessary to recognize the risk of infection. *Conclusion:* C1q nephropathy is considered to be a heterogeneous disease group from the clinicopathological point of view. In order to treat established C1q nephropathy, it is necessary to clarify the pathological significance of C1q deposition in glomeruli. As it was initially refractory to steroid treatment, CMV infection was strongly considered. When administering high doses of steroids, it is necessary to recognize the risk of infection.

Keywords: C1q Nephropathy, CMV Infection, Children

1. Introduction

C1q nephropathy occurs when C1q is significantly deposited in the mesangial region and systemic lupus erythematosus has to be excluded before the diagnosis can be made [1, 2]. On light microscopy, C1q nephropathy may manifest as minimal change disease and focal glomerulosclerosis; however, its characteristic deposits are observed only in the mesangial region under electron microscopy. Many cases manifest as nephrotic syndrome in their teens to 20s and are often steroid-resistant or steroid-dependent. [2, 5-7] However, C1q nephropathy is a controversial condition and is poorly understood. Furthermore, there are many aspects related to C1q nephropathy, which are not certain.

We report a case of a 2-year-old boy who was diagnosed with steroid-resistant C1q nephropathy. As he was initially managed as a case of idiopathic nephrotic syndrome, prednisolone was administered. However, as his condition

did not improve with steroid treatment, other causes for nephrotic were considered, including infections. Based on the histological findings, C1q deposition was noted in the mesangium, which confirmed the diagnosis of C1q nephropathy. Cyclosporine A was initiated, which resulted in complete remission from the disease.

2. Case

A 2-year-old Japanese boy developed progressively worsening edema of both eyes, decreased urine output, and wheezing triggered by colds. He was referred to a hospital on suspicion of nephrotic syndrome. His laboratory results were as follows: serum albumin, 1.2 g/dL; urine red blood cell (RBC) count, 20–29/ high power field (HPF); and urine protein/creatinine ratio (UPCr), 22.75 g/gCre. He was initially diagnosed with idiopathic nephrotic syndrome, and treatment was initiated with prednisolone (PSL) 2 mg/kg/day. On the 15th day after the start of treatment, his condition

improved, and his UPCr was 1.06. However, colds were noted the next day, and his U-pro worsened. He was continuously treated with PSL for 4 weeks; however, disease remission was not achieved. Hence, he was referred to our hospital with a diagnosis of steroid-resistant nephrotic syndrome (SRNS). There was no family history of any kidney disease. He had no symptom of infection in the last few months, and his vital signs were normal. His height was 78.3 cm, and weight was 11.3 kg, which was his normal weight. Physical examination showed that he had no marked generalized edema, cutaneous purpura, abdominal pain, or joint pain and skin findings.

His laboratory results upon referral were as follows: serum total protein, 5.8 g/dL; serum albumin, 2.8 g/dL; aspartate aminotransferase, 26 IU/L; alanine aminotransferase, 28 IU/L; lactate dehydrogenase, 332 IU/L; alkaline phosphatase, 410 IU/L; total bile acid, 1.1 μ mol/L; ammonia, 33 μ g/dL; total cholesterol, 307 mg/dL; triglyceride, 79 mg/dL; blood urea nitrogen, 10.5 mg/dL; serum creatinine, 0.23 mg/dL; sodium, 139 mEq/L; potassium, 4.3 mEq/L; chloride, 106 mEq/L; calcium, 8.8 mg/dL; and C-reactive protein, 0.02 mg/dL. Immunological examination revealed serum IgG of 383 mg/dL, serum IgA of 114 mg/dL, C3c of 134.4 mg/dL (normal range: 73–138 mg/dL), C4 of 33.2 mg/dL (normal range: 11–31 mg/dL), CH50 of 48 U/mL, and antistreptolysin O of 10 IU/mL. Antinuclear, myeloperoxidase, and proteinase 3 antineutrophil cytoplasmic antibodies were negative. white blood cell count, 11,800/ μ L; hemoglobin, 14.6 g/dL; Urinalysis and urine chemistry results were as follows: urine RBC, 1–4/HPF; UPCr, 4.39 g/gCre; and urinary β 2-microglobulin, 310 μ g/L. The serological tests for HBsAg, anti-HBsAg, anti-HCV, anti-neutrophil antibody, human immunodeficiency virus, and perinuclear anti-neutrophil cytoplasmic antibody were negative. These results did not meet the diagnostic criteria for SLE at the first visit to our hospital.

Notably, atypical lymphocytes were found in the blood sample, and it was considered necessary to confirm the presence of an infection. A cytomegalovirus (CMV) antibody titer test and Epstein-Barr virus (EBV) antibody titer test were performed. A negative IgM and IgG with EBV were considered negative for EBV infection and a positive IgM and IgG was considered positive for cytomegalovirus infection. Since the C7-HRP was negative, treatment for CMV was not initiated. Upon admission to our hospital, the dose of PSL was reduced to 1 mg/kg/day. However, since the patient's blood pressure was elevated, lisinopril 0.1 mg/kg/day was administered. One week after admission, proteinuria resolved. A renal biopsy was performed because the CMV infection was speculated to have been caused due to PSL treatment; however, the infection was accompanied by hematuria. The results revealed 24 glomeruli (Figure 1A and B). Additionally, it was found that minimal interstitial inflammatory infiltrates comprised <5% of the renal cortex. Immunostaining studies revealed predominant mesangial staining for C1q (2+), and comparatively lesser staining for IgG (\pm), IgA (–), IgM (1+), C3 (–), and Fib (–) (Figure 2). The pathological findings and clinical renal manifestations

confirmed the diagnosis of C1q nephropathy.

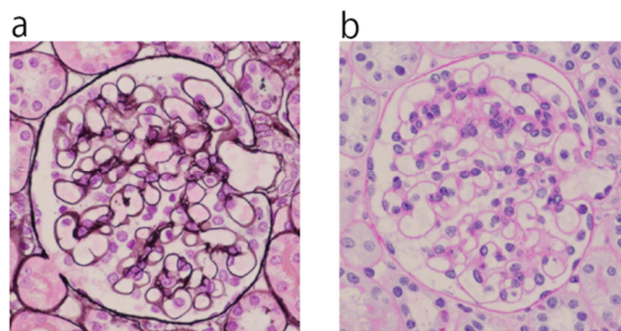


Figure 1. Pathological results of the kidney biopsies.

a) PAS staining b) HE staining (Magnification: $\times 200$)

PAS and HE staining showed nothing increase in mesangial cells/matrix, nothing basement membrane thickening, nothing other abnormal findings in glomeruli, and nothing significant findings in renal tubules/interstitium.

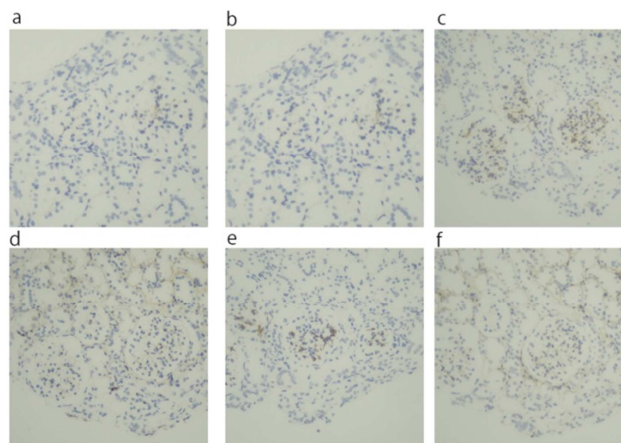


Figure 2. Immunostaining Enzyme antibody studies of the kidney biopsy.

a: IgG immunostaining, b: IgA immunostaining, c: IgM immunostaining, d: C3 immunostaining, e: C1q immunostaining, fibrinogen immunostaining. (Magnification: $\times 200$) Positive deposits of C1q(e) and IgM (c) were detected the mesangial regions dominant and along the capillary walls were also slightly detected.

We attempted to taper the dose of PSL; however, NS recurrence was triggered by colds. Therefore, cyclosporine A (CsA) was introduced, resulting in complete remission for 20 months after completion of CsA therapy. The clinical course of the patient is summarized in Figure 3.

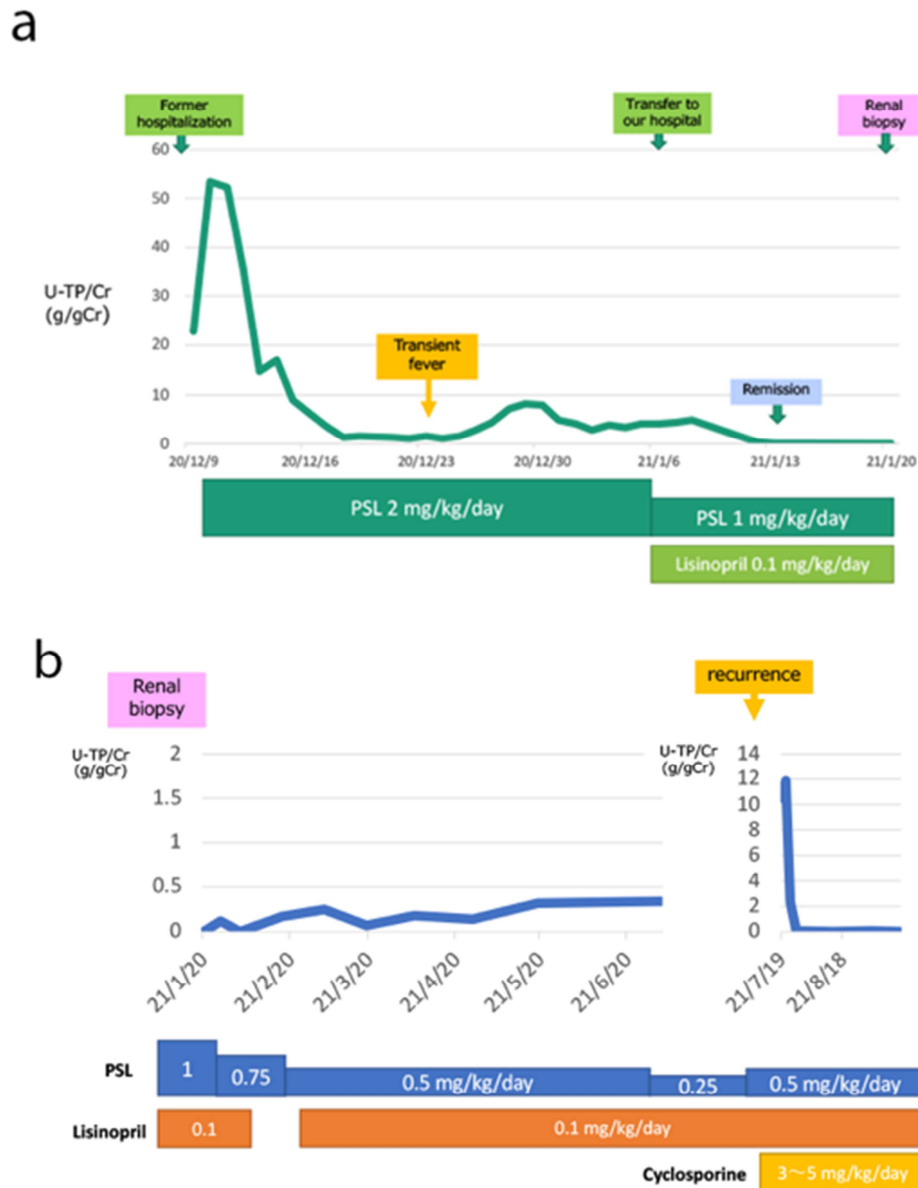
Upon admission to our hospital, the dose of PSL was reduced to 1 mg/kg/day. However, since the blood pressure was elevated, lisinopril 0.1 mg/kg/day was administered. One week after admission, proteinuria resolved. A renal biopsy was performed because CMV infection was thought to have been caused by PSL treatment; however, it was accompanied by hematuria. The results revealed 24 glomeruli (Figure 1A and B). Additionally, minimal interstitial inflammatory infiltrates were found to comprise <5% of the renal cortex.

Immunostaining studies revealed predominant mesangial staining for C1q (2+), with lesser staining for IgG (\pm), IgA (–), IgM (1+), C3 (–), and Fib (–) (Figure 2). The pathological findings and clinical renal manifestations

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Urinary protein/ creatinine ratio (U-TP/Cr), and the treatment during the observation period.

Figure 3. Clinical course.

3. Discussion

The onset of C1q nephropathy often occurs in the teens; however, in Japan, it is often detected early by urine examination in school. [8] The prevalence of C1q nephropathy varies depending on the literature, but it is noted in 0.2% to 16% of all renal biopsy cases. [9] This may be due to differences in race/ethnicity, age, and clinical conditions. In a study of children aged 15–18 years or younger at diagnosis, the average age of onset tended to be higher in older children (around 10 years old). Additionally, in studies

that included adults, the age onset tended to be higher in young adults. [9] There are also reports that younger people have poorer renal prognosis. [10]

As for clinical findings, proteinuria was found in almost all cases in all reports, and nephrotic syndrome was also found in more than half of the reports. Hematuria less frequently occurs than proteinuria, but there are cases wherein gross hematuria was observed [10, 11]. Meanwhile, asymptomatic cases were frequently reported in Japan. [10, 11]

The renal histological findings showed MCD, MesPGN, and FSGS on light microscopic examination, and some showed MPGN and membranous nephropathy.

Patients with nephrotic syndrome or severe proteinuria were also treated with steroids, with outcomes ranging from those with normal urinary findings to those with end-stage renal disease. [10, 11]

C1q nephropathy was reportedly related to viral infections, including Epstein–Barr virus (EBV), CMV, and hepatitis B/C. However, its definite cause remains unknown. [12]

Proteinuria is the main clinical symptom, and about half of cases develop NS, as in this case. However, it was reported that the 5-year renal survival rate is 50% when NS develops. [4]

In addition to MCD, various pathological findings, such as FSGS, Mes, and MPGN, are observed. However, a finding of FSGS increases the risk of renal failure. [9]

Currently, there is no standard treatment for C1q nephropathy, and treatment is centered around PSL and immunosuppressants. In our case, PSL alone failed to achieve remission. Thus, CsA was added to the treatment regimen.

The pathogenic significance of C1q deposition in the glomerulus remains unclear.

Although C1q is the first component of the classical complement activation pathway, it remains unknown whether the complement cascade in C1q nephropathy is activated.

Markowitz *et al.* [3] did not find hypocomplement hemorrhage or other systemic diseases in patients with C1q nephropathy who presented with nephrotic syndrome on

histological MCD/FSGS. From this, it was speculated that the deposition of C1q was due to the enhancement of nonspecific uptake in the mesangium associated with proteinuria. It was speculated that it was due to the accompanying increase in nonspecific uptake in the mesangium.

Hisano *et al.* also showed the urinary findings and exacerbations in cases wherein C1q deposition resolved following repeat renal biopsy. Additionally, they noted that C1q nephropathy was associated with diseases such as MCD, MesPGN, and FSGS. Furthermore, they hypothesized that C1q deposition may have only occurred in the mesangial region. [11]

C1q nephropathy is histologically divided into the category of MCD/FSGS and immune complex nephritis such as MN and MPGN. Clinically, it varies from mild proteinuria to nephrotic syndrome and gross hematuria. Therefore, C1q nephropathy is considered to be a heterogeneous disease group from the clinicopathological point of view. Overall, eight cases of C1q nephropathy under the age of 2 years have been reported, including our case.

Table 1 summarizes the clinical features, pathological findings, and treatment details of the eight cases. [3, 13, 14] Most of the cases had similar characteristics as those of older children, but there were also cases of crescent-forming glomerulonephritis that rapidly resulted in renal failure as well as cases of congenital nephrotic syndrome. [13, 14]

Table 1. Clinical characteristics of patients diagnosed and treatments with C1q nephropathy.

	age	sex	NS	Urinary pro/cre g/gCre)	hematuria	eGFR ml/min/1.73)	ANA	complement
1	1month	F	+	NA	-	NA	NA	NA
2	1year 2months	M	+	69.7	-	52.3	NE	Normal
3	1year 7months	F	+	19.7	+	200	-	Normal
4	2years	F	+	15.8	-	174	-	normal
5	2years	M	+	NA	-	39	NA	NA
6	2years	M	+	NA	+	56	NA	NA
7	2years	M	+	22.8	+	111	-	normal
8	2y	M	+	65.3	-	75	-	normal

Table 1. Continued.

	LM	IF	EM	treatment	outcome	Reference
1	MC	C1q:3+, C3:1+, IgG:2+, IgA:±, IgM:1+	mesangial deposits	PSL	CR	13
2	SCG	C1q:3+, C3:4+, IgG:3+, IgA:1+, IgM:3+	mesangial deposits	PSL, ACE-I	ESRD	4
3	MC	C1q:2+, C3:1+, IgG:±, IgA:±, IgM:1+	mesangial deposits	PSL, CsA	CR	14
4	MC	C1q:3+, C3:1+, IgG:2+, IgA:±, IgM:2+	paramesangial deposits	MPT, PSL, ACEI, CsA	CR	4
5	MC	C1q:4+, C3:1+, IgG:2+, IgM:2	NE	MPT, PSL	ESRD	14
6	MC	C1q:2, C3:0, IgG:1, IgM:0	NE	PSL	CR	14
7	MC	C1q:3, C3:±, IgG:±, IgA:±, IgM:1+	NE	PSL, CsA	CR	This case
8	MC	C1q:3+, C3:1+, IgG:2+, IgA:±, IgM:2+	NE	PSL, ACE-I	CR	our experience

Abbreviation: M; male, F; female, MC; minimal change, SCG; severe crescentic glomerulonephritis, PSL; prednisolone, MPT; methylprednisolone pulse therapy, MC, CsA; cyclosporine A, ACE-I; angiotensin converting enzyme inhibitor, CR; complete remission, ESRD; end stage renal disease, NE; not examined, NA; not available.

Treatment is mostly consistent of oral steroids, steroid pulse therapy, immunosuppressants, and ACE inhibitors.

The outcome was renal failure in two of the eight cases. Due to the small number of cases, it remains unclear whether younger children have more prognostic factors. However, it seems certain that a decreased renal function and unfavorable pathological findings are poor prognostic factors.

Although no clinical symptoms of CMV or EBV were noted, tests for these infections were performed because proteinuria relapsed after transient fever, and atypical lymphocytes were detected from the time of admission. The result was CMV-IgG (+)/IgM (+), which was considered as a complication of CMV infection.

AS C7-HRP was negative, GCV was not administered, and

PSL dose reduction resulted in resolution of proteinuria within 1 week.

From the above process, it is considered that the remission of NS was not obtained due to CMV infection rather than SRNS.

PSL has various immunosuppressive effects such as cell-mediated immunity, humoral immunity, and decreased cytokine production.

According to reports from adult SLE patients, the risk of infection, especially opportunistic infections such as CMV, due to PSL increases in a dose-dependent manner. [15]

During NS treatment, it is necessary to fully recognize that the patient is in an immunocompromised state due to high-dose PSL. As such, clinicians should be aware of the high risk of infection in cases wherein there is a poor therapeutic effect.

4. Conclusion

We report a case of a 2-year-old boy who was diagnosed with C1q nephropathy. Due to the small number of cases, it remains unclear whether younger children have more prognostic factors. However, it seems certain that a decreased renal function and unfavorable pathological findings are poor prognostic factors.

C1q nephropathy is considered to be a heterogeneous disease group from the clinicopathological point of view. In order to treat established C1q nephropathy, it is necessary to clarify the pathological significance of C1q deposition in glomeruli.

As it was initially refractory to steroid treatment, CMV infection was strongly considered. When administering high doses of steroids, it is necessary to recognize the risk of infection.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

Ethical approval from the administrative and the research committee in the hospital was obtained.

Consent

Written informed consent was obtained from the parents of this patient for the publication of this case report and any accompanying images.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Contribution of Each Author

RO, KF, SK and HT treated the patient. HN and HT performed the analysis. RO wrote the paper.

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