—Case Reports—

An Infantile Case of Early Manifestation of SLE-like Symptoms in Complete C1q Deficiency

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Abstract

C1q deficiency is a rare complement deficiency in the early part of the complement cascade. Patients with C1q deficiency have severe recurring life-threatening infections and systemic lupus erythematosus (SLE)-like symptoms. We report on a boy with recurrent life-threatening infections and SLE-like recurrent skin conditions before 2 years of age. Immunological studies revealed an undetectable level of C1q. No abnormality was observed in the urine, but renal biopsy showed segmental granulonephritis. However, the changes observed were atypical for SLE nephritis. This case of C1q deficiency was unusual because the SLE-like symptoms appeared earlier than that normally seen in complement deficiency. Therefore, this case provides insights into the development of autoimmune disease, particularly in the early phase of component deficiency, and in managing renal disease that may develop in the future.
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Key words: C1q deficiency, systemic lupus erythematosus, classical pathway, complement

Introduction

Primary immunodeficiency diseases are rare but significant as they allow us to understand the mechanism and development of the immune system in childhood. Complement deficiency increases the risk of autoimmune disease, especially that of systemic lupus erythematosus (SLE), and results in frequent and severe infections. Deficiencies have been reported of almost all components of the complement cascade (C1–C9) as well as of the activator or inactivator in the complement cascade. The various clinical features help elucidate how autoimmune diseases develop. Deficiencies of the components of the classical complement pathway (C1q, C1r, C1s, C2, and C4) result in a high risk of SLE-like symptoms in childhood[1] and lead to increased susceptibility to severe recurrent infections. C1 is composed of 3 distinct subunits: C1q, C1r, and C1s. Congenital C1q defects are mainly classified into 3 groups: partial, complete, and functional. Thus far, complete defects of C1q have been reported in individuals 5 to 37 years of age[2]. More than 90% of patients with homozygous C1q deficiency exhibit SLE-like symptoms, whereas 50%

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of patients with C1s and C1r deficiencies have SLE-like symptoms[3,4]. Homozygous C2 deficiency, which is the most common deficiency (1/30,000 among whites) in the classical complement pathway, is associated with SLE in 10% to 30% of patients, with a mean age of 37 years at diagnosis[5]. Although the understanding of complement deficiencies greatly contributes to the elucidation of the function of the immune system, the mechanism by which C1q prevents the development of SLE-like symptoms remains unclear.

In this paper, we report on a boy with congenital C1q deficiency who has had recurrent necrotizing lymphadenitis since 4 months of age and presented with SLE-like symptoms, such as butterfly-type erythema and Raynaud's sign, at approximately 12 months of age. With regard to the timing of the detection of C1q deficiency, severe recurrent infection and the typical signs associated with autoimmune disease usually emerge only in late childhood. Therefore, our case is valuable, as this report documents SLE-like changes and pathological events at an earlier time point than in reports of similar cases.

Case Description

The patient had had recurrent fever and left cervical lymphadenitis since 4 months after birth and required frequent treatment with antibiotics. The treatments were effective each time. At the age of 12 months, butterfly-type erythema and Raynaud's sign became apparent on the face, hands, and feet. At 14 months of age, the patient had cervical lymphadenitis caused by another bacterial infection, and a lymph node biopsy performed at that time led to the diagnosis of necrotizing lymphadenitis. CH 50 was not detectable, and the levels of C3 and C4 were 121 mg/dL and 60 mg/dL, respectively. The antinuclear antibody (ANA) level was 40 times the normal value, and rheumatoid factor (RF) was detected. Because fever recurred and the butterfly-type erythema repeatedly underwent remission and exacerbation, the patient was brought to our hospital at 22 months of age for further evaluation and treatment.

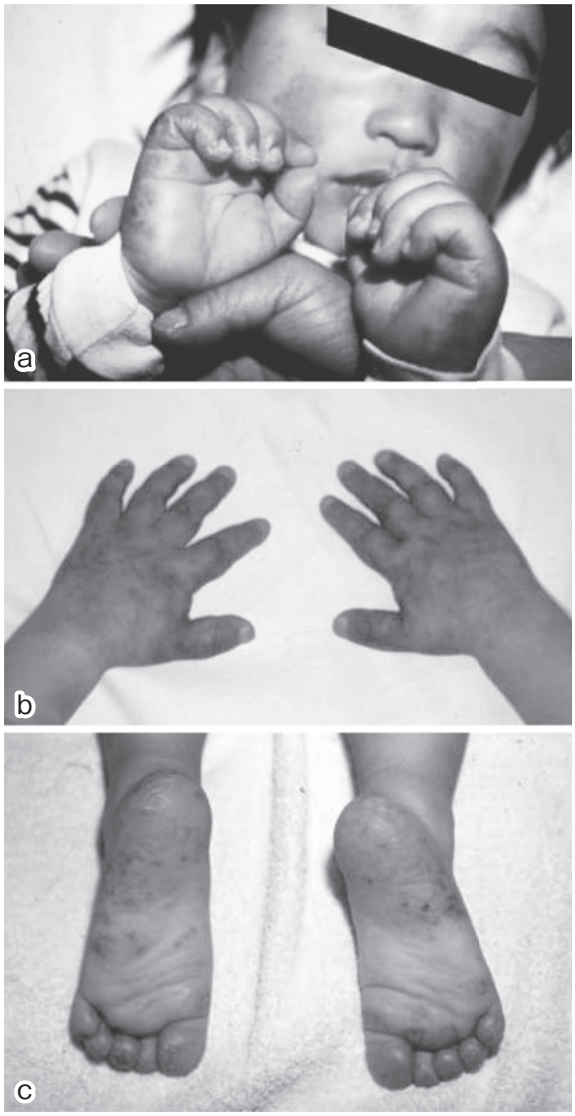

Fig. 1 SLE-like butterfly erythema on the cheeks, soles of the feet, and palms.

The patient's parents were healthy, and there was no family history of any hereditary disease. Other than hyperbilirubinemia at birth, there were no significant events. The height and weight of the child were within the normal ranges. Other than the butterfly rash on the cheeks, feet, and hands (**Fig. 1**), no other signs were observed. Joint swelling was present, but movement was not restricted.

Blood tests showed no anemia or inflammatory reactions, and the results of urinanalysis were normal (**Table 1a**). The karyotype was 46 XY. The serum levels of all immunoglobulin isotypes were normal (**Table 1b**), but the RF level was 171 IU/mL, and ANA was detectable. Furthermore, tests for anti-DNA coagulant, lupus erythematosus (LE) cells,

Table 1a Laboratory findings on admission (1)

Blood cell count		Blood Chemistry		Urinalysis	
WBC	6,000 /μL	AST	30 IU/L	pH	6.5
St	2 %	ALT	35 IU/L	Protein	(−)
Seg	11 %	LDH	529 IU/L	Glucose	(−)
Ly	82 %	ALP	458 IU/L	Occult blood	(−)
Mono	5 %	T-cho	141 mg/dL		
Eosino	0 %	UA	2.5 mg/dL	Serological test	
Baso	0 %	T-Bil	0.8 IU/L	CRP	0.34 mg/dL
RBC	515×10^4 /μL	Na	144 mEq/L	ESR 60 min	2 mm
Hb	13.2 g/dL	K	4.4 mEq/L	Alb	64.3 %
Ht	40 %	Cl	107 mEq/L	α1	1.9 %
Plt	36.1×10^4 /μL	Ca	10.2 mg/dL	α2	11.0 %
		TP	7.3 g/dL	β	10.9 %
		Alb	4.2 g/dL	γ	11.8 %
		BUN	11 mg/dL		
		Cre	0.4 mg/dL	Chromosome	
					46XY

Table 1b Laboratory findings on admission (2)

Immunoglobulins		CH50	1.7 U/mL
IgG	863 mg/dL	ASO	50 IU/mL
IgA	97 mg/dL	RF	171 IU/mL
IgM	192 mg/dL	ANA	(±)
IgE	27 mg/dL	Anti-DNA	(−)
		LE test	(−)
Lymphocyte subsets (peripheral blood)		Immune complex	Not detected below 1.5 ug/mL
		Lymphocyte response to PHA, Con-A, PWM	normal
CD3	54.5 %	Neutrophil function test (02-productivity, opsonophagocytosis)	normal
CD4	32.9 %	ADCC activity	46 % (41–72)
CD8	16.4 %	NK activity	10.0 %
CD20	40.5 %		
CD16	0.9 %		
CD56	1.5 %		
CD57	0.7 %		
HLA-DR	32.7 %		

and immune complexes were negative. Surface marker tests indicated that the percentages of CD20 and human leukocyte antigen (HLA)-DR, which are associated with B cells, were increased, whereas the percentage of natural killer (NK) cells (CD56-, CD57-, and CD16-positive cells) were decreased. The antibody-dependent cell-mediated cytotoxicity was 46%, which was within the normal range, whereas NK cell activity was only 1%. Results of the lymphocyte transformation test with concanavalin A, phytohemagglutinin, and pokeweed mitogen were normal. We also determined the O_2 productivity in opsonophagocytosis as a neutrophil function, but the values were the same in both the control serum and the patient's serum. The complement test was as illustrated in **Table 1c**. The CH 50 value was 1.7 U/mL. The C1q protein content was also undetectable as the protein itself with single-radial immunodiffusion and in terms of its activity (with the hemolysis method). Single-radial immunodiffusion revealed high values of C1r and C1s at 176.9% and 161.9%, respectively. Although levels of C2, C4, and C1 inactivator (C1-INA) were high, levels of other complement components were within their normal ranges. C3 nephritic factor (C3-NeF) was not detected, but C1q receptor (E-CR) was detected with

Table 1c Complement data on patient

	22 months	28 months	Normal value (method)
CH50	1.7 U/mL	1.9 U/mL	25.0–48.0 (Mayer)
C1q	N.D.	N.D.	8.7–14.6 (SRID)
C4	36.0 mg/dL	71.0 mg/dL	12–89 (TIA)
C2	2.4 mg/dL	4.4 mg/dL	1.6–3.6 (ID)
C3	91.0 mg/dL	119.0 mg/dL	86–160 (TIA)
C5	15.1 mg/mL	13.4 mg/dL	8.0–15.0 (TIA)
C6	3.7 mg/dL	4.0 mg/dL	2.7–4.3 (SRID)
C7	5.0 mg/dL	2.2 mg/dL	1.9–5.3 (SRID)
C8	8.3 mg/dL	8.6 mg/dL	4.9–9.2 (SRID)
C9	5.8 mg/dL		2.0–7.1 (SRID)
Factor B	26.8 mg/dL		12.2–32.2 (SRID)
C1-INA	25 mg/dL		25–259 (ID)
C3-NeF	(−)		
E-CR1	88.6 mg/dL		70> (Flow)

N.D.: not detected, SRID: single radial immunodiffusion test, TIA: Turbidimetric immunoassay, ID: immunodiffusion test

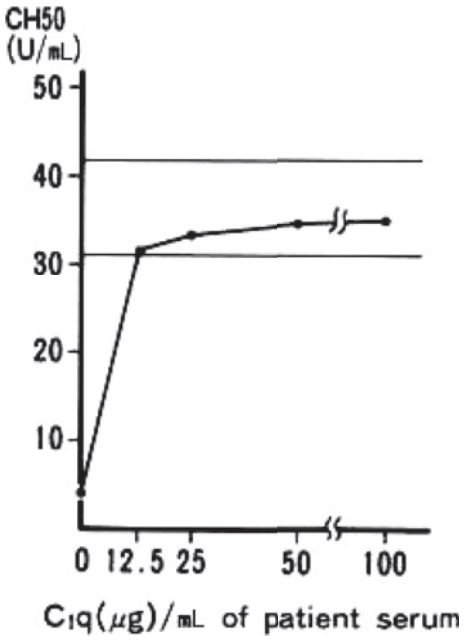

Fig. 2 This figure presents the results of the CH 50 reconstitution test. We added purified C1q to the patient's serum at 37℃ for 30 minutes. When C1q was added to the patient's serum, the CH 50 was reconstituted to the normal level, and this value remained constant with the addition of C1q.

flow cytometry. We also examined the serum complement levels of the patient's parents. The levels of C1q and other components of the complement cascade, except for C7 in the patient's father, were normal. Furthermore, the CH 50 level of the parents was within the normal range (father, 42.4 U/mL, and mother, 39.6 U/mL).

We examined the antigen-antibody reaction against the C1q antibody to the patient's serum by means of Ouchterlony analysis[6]. No bands were seen in the plate. We then added purified C1q to the patient's serum at 37℃ for 30 minutes and then examined the CH 50 level. The CH 50 level was within the normal range **(Fig. 2)**. These results suggested that our patient had complete C1q deficiency and not partial deficiency.

At 3 years of age, the patient had prolonged fever, severe exanthema, and stomatitis. The condition of the skin was so severe that a biopsy was performed. Necrotic epidermal cells and desmol edema were observed with atrophic change. Hydropic degeneration was present in the basal layer, and IgG, IgM, IgA, and C3 were observed, but no C1q was present in the dermis; these results were equivalent to the pathological finding of a patient with SLE. Although neither hematuria nor proteinuria was observed, C1q deficiency often causes nephritic change, and we thought a renal biopsy would help evaluate the status and prognosis of nephritic changes, if present. A renal biopsy was performed when the patient was 4 years old with the informed consent of the parents. Interestingly, histopathologic diagnosis was inconsistent with the symptoms of the skin: the biopsy revealed segmental

mesangiopathic glomerulonephritis; IgG, IgA, IgM, and C3 were deposited in the mesangial lesion; and IgG, IgA, and IgM were deposited in the glomerular basement membrane. At this time, the patient began to experience physical limitations of the hands and ankles.

Discussion

In this report we present a rare case of C1q complete deficiency with accurate differential diagnosis in early childhood, with a description of the development of SLE-like symptoms.

C1q deficiency is a rare deficiency of early complement component. According to a database of primary immunodeficiency in Japan up to 2007 (http://pidj.rcai.riken.jp/public_shoureisu.html), only 14 cases of complement deficiency of all types have been reported in children, accounting for 2.3% of all cases of congenital immunodeficiency. In the 1970s, the first cases of complement deficiency were reported as complications of severe immunodeficiency[7] or Bruton-type X-linked hypogammaglobulinemia[8]. Berkel et al. first reported on a 10-year-old boy with complete C1q complement deficiency[9]. Loos et al. have classified C1q deficiency into 3 types: partial deficiency, complete deficiency, and dysfunction of the C1q complement[10]. Thereafter, acquired C1q deficiency was included as the fourth type; this type of deficiency may occur due to autoantibodies (anti-C1q antibody) or excessive C1q consumption leading to chronic immune complex activation[11]. Normally, C1q functions in the binding of immune complexes and apoptotic cells and contributes to their removal from the circulation.

More than 90% of patients with C1q deficiency exhibit SLE-like skin symptoms, whereas only 60% to 75% of patients deficient in other components of the classical pathway exhibit such symptoms[4]. Common skin changes similar to those of SLE, such as butterfly-type erythema and discoid-type lesions, are observed. In some cases skin biopsy shows the presence of C3 or IgG deposits in the dermoepidermal junction. In the present case, similar SLE-like exanthema was observed, and skin biopsy revealed edema necrosis in the epidermis and hydrophilic degeneration in the basal layer. Unfortunately, immunostaining of this area was not performed, but the observations agreed with the results of skin biopsy in patients with SLE. However, the SLE-like symptoms in patients with complement deficiency develop at a younger age than in patients with SLE. The average age of onset of SLE-like skin symptoms in complement deficiency is 7 years and such symptoms are more likely to develop in male patients[4]. However, why SLE-like symptoms are observed in complement deficiencies remains unknown. C1q binds to the Fc component of IgG or IgM and apoptotic cells, and then the lack of interaction of complement with immunoglobulin and these cells might prevent cell clearance, leading to the production and buildup of autoantibodies[12,13].

With regard to effects of complement deficiency on the kidneys, the nephritic changes in C1q deficiency differ from typical lupus nephritis because of the presence of mesangioproliferative glomerulonephritis and IgM deposits in the component. Abnormal changes cannot be detected in urine, but our patient underwent renal biopsy at the age of 3 years. The histopathologic diagnosis was in agreement with these results: IgG, IgA, IgM, and C3 were found in mesangial lesions, and IgG, IgA, and IgM were found in the glomerular basement membrane. Although our patient was too young for lupus nephritis to have developed, the results differed from those typical of a case of SLE. These results are interesting and can provide insights into the development of nephritis in patients with C1q deficiency.

Because of the inability of clearance by immune complexes, patients with C1q deficiency are also at increased risk for severe infection, particularly by encapsulated bacteria, such as Streptococcus pneumoniae, which would trigger an autoimmune disease. Similarly, our patient also had recurrent infections. In patients with C1q deficiency, susceptibility to bacterial infection is greatest during infancy because of the immaturity of the immunological reaction. After the immunological response develops with age, alternative pathways are used to combat infection; however, the surplus of

immune complexes is a sign of autoimmune disease. Finally, the excessive immune complexes accumulate in the kidney in old age.

In addition to our report, other case reports have demonstrated that the serum levels of CH 50 and C1q are almost zero, whereas those of C2, C4, and C1-INA are high. This finding suggests that other early components have compensated for the C1q deficiency. Our patient also had high levels of C2, C4, and C1-INA. The tests for ANA, RF, and C1q-binding immune complexes were positive, and tests for anti-DNA antibody and LE cells were negative. These results are in contrast to those observed in SLE and indicate that the mechanisms of autoantibody production differ even though the clinical observations are similar. On the other hand, anti-Smith antibodies, which are considered specific to SLE, were found to be positive in our C1q deficiency patient; this result requires further exploration. The finding of the low number and activity of NK cells has not, to our knowledge, been reported in any other case. Patients with SLE tend to exhibit low NK cell activity, as well as low interleukin (IL)-2 activity, which might cause the low NK cell activity. However, the precise mechanism of the reduced IL-2 activity in SLE remains unclear. Unfortunately, we did not measure IL-2 activity in our case, but lower IL-2 levels might be a secondary response in patients with C1q deficiency.

In a patient with C1q deficiency, the infection and autoimmune symptoms, particularly those in the kidney and the central nervous system lupus, determine the patient's quality of life. There is no curative therapy. Fresh-frozen plasma has been used in an attempt to restore C1q levels in a patient with C1q deficiency, but the C1q level dropped within hours after transfusion[10]. Following exposure to a "foreign" protein, antibodies may develop and rapidly deplete infused C1q. Some studies have tried to evaluate the possibility of bone marrow transplantation (BMT)[14,15]. C1q model mice can modulate C1q levels in serum and were clinically cured by BMT, but further data are required before human trials can be started. Furthermore, the titer of autoantibodies and the development of glomerulonephritis in the lupus-prone mice can be attenuated by manipulating the level of C1q expression by BMT[14]. These findings suggest BMT is a potential treatment for patients with C1q deficiency. The localization of C1q is composed of 3 polypeptide chains, all of which are products of the corresponding individual 3genes clustered on human chromosome 1[16]. Seven individual mutations have been reported[17,18]. We did not identify the gene mutations in our patient, but a specific mutation might have accelerated the development of SLE-like symptoms.

Here, we have reported on a patient with complete C1q deficiency. Such C1q deficiency is rare, and our case report is important because SLE-like symptoms developed at an early age. When SLE-like symptoms are noted in infants, both autoimmune disease and complement deficiency must be considered as possible causes. Our patient has segmental glomerulonephritis, which, fortunately, has not progressed to renal failure or an acute central nervous system SLE-like vasculitis. Further follow-up may elicit new findings and help elucidate the mechanism of complement production.

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