Case Report

A Case of Hereditary Angioneurotic Edema Associated with Systemic Lupus Erythematosus

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A pedigree of C1 inhibitor (C1 INH) deficiency associated with positive LE cell and an elevated titer of DNA antibodies and antinuclear factor (ANF) and nephropathy was presented. The proband of this family was diagnosed as having definite systemic lupus erythematosus (SLE) after a clinical course of several year since her first visit to our hospital and because of the lack of hemolytic activity of complement (CH50), in spite of the absence of idiopathic edema, C1 INH levels were 1.2 mg/dl (3.8% NHS) determined as antigen and 65 site forming unit (SFU) (5.8% NHS) determined by hemolytic assay in her blood. Her mother and brother had characteristic idiopathic edema of her face, larynx, hand and bowel and they had low levels of C1 INH of 1.8 mg/dl (5.8% NHS) and 4.8 mg/dl (15.5% NHS) respectively in their blood. On the basis of these findings, this family was diagnosed as having a pedigree of hereditary angioneurotic edema (HANE) which is supposedly an inherited autosomal positive trait. Actually, however, the proband's serological and hematological indices became positive and progressed year by year, which implies that SLE was absent for the first several years. It might be said that this interesting clinical course indicates that SLE appeared chronologically as a hereditary deficiency in one of the complement components in this case. In concurrence with the general observation that recurrent viral infections due to the deficiency of complement components are presumed to be responsible for SLE-like disease. Her levels of several kinds of anti-virus antibodies were high. Methylprednisolone helped normalize her level of C1 INH and ameliorate the clinical course.

Key Words: C1 inhibitor deficiency, Hereditary angioneurotic edema, Systemic lupus erythematosus, Anti DNA antibody, LE cell, Membranoproliferative glomerulonephritis, Virus titer

The systemic lupus erythematosus (SLE)-like symptom is one of the most prominent features associated with complement component deficiency. Especially, the symptom is well known to be associated with C1 inhibitor (C1 INH) deficiency¹⁻⁵. However, although the patients' symptoms seem clinically like SLE in some respects, usually they do not satisfy all of the major diagnostic criteria for SLE.

Agnello⁴) stated that the characteristics of the lupus-like disease differ from those of classic lupus in the following points: (1) the increase incidence of discoid lesions, (2) the low incidence of renal disease, (3) the low titers or absence of antibodies to native DNA, and (4) the infrequent finding of

immunoglobulin and complement in the skin lesions.

It is well known that persons with C1 INH deficiency have the clinical symptoms of hereditary angioneurotic edema (HANE). The first case of HANE associated with SLE was reported by Kohler²) in 1974 after a case report of HANE with erythema marginatum-like lesion without systemic change⁶).

Recently, very interestingly, a case of C1 INH deficiency associated with SLE, satisfying the major diagnostic criteria for SLE of the American Rheumatism Association (ARA), was found in a pedigree of HANE. Besides lupus erythematosus (LE) cells, antinuclear factor (ANF) and anti-

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native DNA antibodies were present in this case. Especially the antibody titers against various viruses were highly elevated. This finding is very important because makes it possible to speculate on the pathogenesis of the development of SLE in relation to the complement component deficient state.

CASE REPORT

A 33-year-old unmarried woman was the proband. She had a history of a subcutaneous abscess after receiving a injection at 6 years old (y.o.) and underwent an appendectomy at 13 y.o. At age 14, SLE was suspected because of a fever (39°C) with arthralgia and erythema of her face, but it was not serologically demonstrated. Corticosteroid was administered at age of 15, at St Luke's Hospital.

In April 1967 at age 17, she visited our hospital complaining of a high fever and facial erythema. SLE was suspected from the facial erythema and high erythrocyte sedimentation rate in spite of the absence of LE cells. Four mg of betamethasone

was administered daily during her first stay in our hospital from July 6 to September 11, 1967.

She was hospitalized again for Libman-Sachs' pericarditis from May to August 1968. In April 1969, she attempted suicide by means of a large amount of sedatives, but recovered after gastric lavage. In July 1970, the LE test became positive and in January 1972, ANF was revealed to be positive with a titer of 320. Between 1970 and 1974, her condition was controlled by the administration of corticoid and she had no complaints except slight facial erythema.

In April 1975, she passed protein and red blood cells (RBC) in her urine. This was the first positive urine finding and thereafter protein and RBC gradually increased in her urine. On June 12, 1976, anti DNA antibody titer of her serum was 83 U/ml (normal value is below 24). On July 4, 1977, a diagnosis of SLE was made, which satisfied the criteria of the ARA since her LE cell test was converted to positive.

On September 26, 1977, it was found that her total hemolytic activity of serum complement

$$\begin{array}{c|c} a & \\ \hline b & c \end{array}$$

Fig. 1. a. Light microscopy (PAS staining, 1×400)
b. Fluorescence microscopy (Anti-C1q serum fixation)
c. Electron microscopy

(CH50) was 4 u/ml and C4 protein was 0 mg/ml. Her mother (50 y.o.) and also her brother (27 y.o.) had idiopathic edema of the unilateral forearm and hand at this time.

At the time of her third hospitalization at age 29, from September 20 to December 18, 1978, her proteinuria markedly increased to 1620 mg/ml. Renal biopsy revealed membranoproliferative glomerulonephritis (MPGN) by light, Fluorescence and electron microscopy as depicted in Figure 1.

In April 1980, she was admitted for the fourth time, because clinical symptoms of SLE were aggravated by anasarca, and bilateral pleural effusion occurred. The daily dose of methylprednisolone was increased to 60 mg t.i.d. to ameliorate the symptoms and she was discharged in January 1981 with an alternate day dose of 52 mg. During this hospitalization, it was found that her mother, brother and aunt as well as herself had a low C1 INH protein level; their levels were 1.8 mg/ml, 4.8 mg/ml, 7.0 mg/ml and 1.2 mg/ml respectively (normal range is 31 ± 10 mg/ml, $M \pm 2SD$). Proband's serological and complementological studies at this hospitalization were

shown in Table 1. Thus it was considered that this family had a pedigree of HANE because they had exceptionally low levels of C1 INH protein in common, although the proband had no clinical history of idiopathic edema.

During the following 3 years, she was apparently healthy as one of our outpatients. She had, however, a fifth hospitalization from January 4 to March 17, 1984, because of aggravated facial erythema and a lethargic feeling. The CH50 level in the serum became as low as 2 u/ml and she had positive LE cells again, probably because of excessive reduction in the dose of methylprednisolone to 32 mg on alternate days. The first examination for dsDNA revealed a titer of 1:40.

Physical examination at the time revealed the following: She was somewhat depressed mentally. Her general condition was apparently not very good, with 154 cm length, 51 kg Bwt, 124/84 BP and 76/min regular PR. She had erythema over the bilateral malar region. Right divergent strabismus was noticed. No struma was felt. The liver, spleen, kidney and lymphatic nodes were not palpable. No skin eruption except on the face was found. Neither edema of the extremities nor cyanosis was found. The cardiopulmonary system was normal when examined by roentgenography and electrocardiography. No abnormality was detected by neurological examination. Neither deformity nor pain was found in any area.

With an increased dose of methylprednisolone, 48 mg every day, she recovered rather easily to a good condition, namely the CH50 returned to the normal range and LE cells disappeared.

On August 4, 1984, she was admitted for the sixth time because of the same condition as above at alternate day dose of methylprednisolone of 64 mg. At this time, methylprednisolone was increased to 48 mg every day. On September 22, she was discovered dead in her bed when she went back to her home temporarily.

Figure 2 shows the proband's clinical course covering the 17 year's progression of her disease. Urinary protein and microhematuria are also depicted.

The pedigree chart of this family is shown in Figure 3. Four family members whose C1 INH

Table 1. Proband's serological and complementological studies

Erythrocyte sedimentation rate	45	mm (1 h)
CRP	5+	
RA	2+	
Protogram		
alb.	49	%
alpha 1 glob.	5	%
alpha 2 glob.	8	%
beta glob.	11	%
gamma glob. (abnormal band at slow gamma)	26	%
CH50	<4	u/ml (normal 30-50)
C1q	73	% (normal 74-126)
C4	2	mg/dl (normal 12-60)
C3	35	mg/dl (normal 36-90)
C5	102	% (normal 70-130)
C9	96	% (normal 83-117)
B	10.8	mg/dl (normal 8-24)
C1 INH	1.2	mg/dl (normal 21-41)
ANF titers	1:320	(normal <1:10)
DNA antibodies titers	152	u/ml (normal <24)
dsDNA antibodies titers	1:40	(normal <1:5)
Sm antibodies	(-)	
RNP antibodies	(-)	
ENA antibodies titers	<1:100	(normal <1:100)
IgG	2360	mg/dl (normal 800-1800)
IgM	236	mg/dl (normal 130-290)
IgA	102	mg/dl (normal 100-180)
Circulating immune complex	(-)	
Serologic test for Syphilis	(-)	
Cryoglobulin	(-)	
LE cell	(+)

Fig. 2. The proband's clinical course over 17 years since her first visit at our hospital.

Pedigree chart of K family

Fig. 3. Pedigree chart of K family

Complement profile (hemolytic assay, % normal) of K family

Fig. 5. The complement profile (hemolytic assay, % normal) of the family (the proband, mother, brother and aunt)

Complement profile of the family

Fig. 4. The complement profile of the family (the proband, mother and brother)

protein levels in the serum were measured had low levels as stated above (II-6, II-7, III-1, III-2

in Figure 3).

The results of the family study of the complement profiles are depicted in Figure 4 and 5. Figure 4 represents the chronological CH50 and serum protein concentration of complement and Figure 5 represents the hemolytic assay by percent at the third admission in 1979. Concerning the proband and her mother, the complement profiles by protein concentration and hemolytic assay coincided well with those of typical HANE, namely low C1 INH, low early component and

substantially normal late component of the complement system.

In the study of the family, there were no consanguineous marriages of the parents or the grandparents of the proband. Her mother had a history of breast cancer at the age of 49, had herpes zoster at the age of 46, appendectomy at age 17 and occasional edema of the face, larynx, bowel and hand but no sign of SLE was detected except a high erythrocyte sedimentation rate (87 mm/hour) without corticosteroid therapy. She had no history of abortion (II-6). The proband's brother, an apparently healthy policeman, has no history of any illness but he had an attack of edema of unilateral hand and forearm after practicing Kendo (Japanese style fencing). On other occasion, he too, sometimes had facial, laryngeal and bowel edema (III-2). Her aunt is an apparently healthy single woman and has no history of edema in spite of a pathologically low level of C1 INH protein (II-7). Three of her six aunts died of infectious diseases such as peritonitis (II-8) and pulmonary tuberculosis (II-10, II-12). Interestingly, the proband and her mother had a history of appendectomy which is often performed because bowel edema of HANE is sometimes misdiagnosed as acute appendicitis.

The three family members shown in Figure 5 had no LE cells (II-6, II-7, III-2 in Figure 5).

DISCUSSION

SLE-like diseases associated with complement deficiency are rather rare⁷⁾. On the other hand, it is reported that SLE-like disease is mostly found in association with C2 deficiency⁸⁻¹⁰⁾. It is also known that diseases associated with complement deficiency are largely divided into two categories. Namely, a deficiency of early component is associated with collagen disease, especially with SLE-like disease, and in general that of the late components is frequently associated with severe fetal infections, and disseminated gonococcemia or recurrent gonococcemia are often seen in the state of deficiency of late components like C5, C6, C7 and C8.

In addition, deficiency of regulator proteins of complement, C3b INH, is reported elsewhere¹¹⁾. Among these regulator protein deficiencies, C1

INH deficiency is rather well known and there are several reports of C1 INH deficiency associated with SLE-like disease¹⁻⁵⁾ and glomerulonephritis¹²⁻¹⁵⁾.

As early as 1974, Kohler²⁾ reported a case of association of hereditary angioedema and familial lupus erythematosus in identical twin boys. This is the first publication of the case of association between HANE and SLE-like disease. Since then, several cases of such association have been reported, as mentioned above. In all these cases, the patients were diagnosed definitely as having HANE on the basis of symptomatology and complementology. Concerning the complement study, their level of C1 INH is markedly low with substantial absence of hemolytic activity and their early levels of components of C4 and C2 are uniformly low. Many reports indicate that the low levels of C4 and C2 predispose the patient to the development of SLE-like disease in some unknown manner. Although the exact pathogenesis of SLE associated with HANE is not fully understood, it is an interesting idea that SLE-like disease is attributable to the lack of virolysis and the inability to eliminate circulating immune complexes from the body under the condition of deficiency of early complement components.

As concern as our case, laboratory findings of the chemical and hematological examination of the proband were almost normal. Data concerning the serological and complementological study are given in Table 1 and show many positive findings supporting the diagnosis of SLE and HANE. It is very interesting that in chronological order, serological and hematological indices for SLE appeared in the pedigree of the genetic disease of HANE as shown in Figure 2.

According to the current hypothesis, a virus is presumed to be the etiologic agent of SLE. The acquired deficiencies of the early components as in the case of HANE would remove the host defense activity against such an organism. Therefore if it is absent, recurrent viral infection with some slow virus would take place easily and consequently the patient would be predisposed to develop SLE. Oishi¹⁶⁾ refers to the high virus antibody titers of sera of patients with SLE-related syndrome with marked hypocomple-

Table 2. Virus antibodies titers of the proband
(May 6, 1980)

Herpes simplex	8	(normal <4)
Herpes zoster	64	(normal <4)
Rubella CF	8	(normal <4)
HI	64	(normal <8)
Measles CF	128	(normal <4)
HI	128	(normal <8)
Adeno virus	<4	(normal <4)
RS	4	(normal <4)
Psitacosis	<4	(normal <4)
Mumps CF	32	(normal <32)
HI	128	(normal <8)
EB	40	(normal <10)
Parainfluenza (1)	<32	(normal <32)
Parainfluenza (2)	<32	(normal <32)
Parainfluenza (3)	<32	(normal <32)

mentemia. Taking this into consideration, it is of great interest that our proband had several-fold increased virus antibody titers as depicted in Table 2.

In the complement-deficiency state, the ability of antigen elimination and solubilization of the immune complex is lacking and consequently we postulate a causative role of circulating immune complexes in the immunopathogenesis of glomerulonephritis in HANE¹²⁻¹⁵). The lack of this ability facilitates the continued existence of circulating or deposited immune complexes resulting in their playing a pivotal role in the development of glomerulonephritis. The most interesting feature concerning the proband was the clinical course of her renal disease. After 8 years of negative findings on urinalysis, microhematuria was first found with the successive appearance of proteinuria and she showed a slight pitting edema in her lower extremities due to the progressive increase in proteinuria and hematuria. Renal histological examination on October 2, 1979, revealed MPGN by light microscopic, FITC-staining and electron microscopic study. Hory¹²⁾, Pickering¹³⁾, Leibowitch¹⁴⁾ and Young¹⁵⁾ reported C1 INH deficiency associated with glomerulonephritis. Our patient also had proliferative glomerulonephritis.

The number of published registered cases of SLE was 13,000 in March 1983 in Japan and the number of families with HANE was at most ten. The possibility of chance of the coexistence

of these two diseases is extremely small.

HANE is not usually treated with methylprednisolone. Danazol¹⁷⁾ increases the C1 INH levels in blood, promoting synthesis in the liver and is indicated for clinical use for treatment of HANE in the United States Pharmacopeia (USP). In our patient, however, the use of methylprednisolone ameliorated her clinical symptoms and laboratory indices of SLE together with increasing her C1 INH level. The prednisolone used at first increased her facial erythema and lethargic feeling. Therefore methylprednisolone is thought to be one of the drugs of choice to treat C1 INH deficiency.

HANE associated with SLE with positive LE cells and dsDNA titer was reported. The full interpretation of the pathogenesis of the association of HANE with SLE, which differs from the association of HANE with SLE-like disease, must await further study. I believe it was possible that in our case, the cause of the SLE was a viral infection resulting from the absence of the complements components under study.

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