Hereditary Angioedema in a Patient With Various Clinical Manifestations of Systemic Lupus Erythematosus: a Case Report

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Abstract

Background: Hereditary angioedema (HAE) is an inherited disease characterized by recurrent angioedema without urticaria or pruritus. The most common types of HAE are caused by deficiency or dysfunction in C1 esterase inhibitor (C1-INH-HAE), which has a reported association with systemic lupus erythematosus (SLE). However, not much is known about the clinical manifestations, disease course, and treatment of SLE complicated with C1-INH-HAE.

Case presentation: A 31-year-old Japanese woman with a history of swelling of the lips without any specific triggers presented to our institution. She began experiencing swelling of the lips at the age of 14 years. At the age of 20 years, she was diagnosed with C1-INH-HAE on the basis of blood test results showing low C4 and C1 esterase inhibitor activity. At the age of 30 years, she developed malar rash, alopecia, and arthralgia in her hands and elbows. In addition, fever, oral ulcers, and discoid rash on the anterior chest were noted at a follow-up examination 8 months later. Physical examination, laboratory tests, and thorough examination of the organ lesions revealed positive antinuclear antibody, fever, nonscarring alopecia, oral ulcers, malar rash, discoid rash, arthralgia, leukopenia, thrombocytopenia, hypocomplementemia, lupus retinopathy, and nephritis. Based on these findings, she was diagnosed with SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria. The patient was initially treated with 20 mg/day prednisolone, and then prednisolone was tapered with the concomitant use of 400 mg/day hydroxychloroquine and 1 mg/day tacrolimus. After the initiation of immunosuppressive therapy, the clinical symptoms associated with SLE improved. At a follow-up examination 7 months later, it was noted that the patient was able to maintain remission of SLE by continuing 7 mg/day prednisolone, 400 mg/day hydroxychloroquine, and 2 mg/day tacrolimus.

Conclusions: Our patient presented with a variety of symptoms, including fever and cytopenia in addition to mucocutaneous, joint, ocular, and renal lesions. It is important for physicians to recognize that SLE complicated with C1-INH-HAE can present with various clinical manifestations and organ lesions.

Background

Hereditary angioedema (HAE) is an inherited disease characterized by recurrent angioedema without urticaria or pruritus [1]. This disease was first described by Osler in 1888 [2]. The prevalence in Europe and the United States is estimated to be about 1 in 50,000, with no racial differences [3].

The most common types of HAE are caused by deficiency or dysfunction in C1 esterase inhibitor (C1-INH) due to abnormalities in the SERPING1 gene (C1-INH-HAE) [4]. In C1-INH-HAE, bradykinin is overproduced owing to activation of the plasma contact system, which increases vascular permeability and causes repeated localized edema in various parts of the body, including the skin, gastrointestinal tract, and respiratory tract. The edema resolves spontaneously and disappears in 2–5 days without treatment; however, laryngeal lesion can cause fatal asphyxia [5].

An association of C1-INH-HAE with autoimmune diseases was previously reported [6–17]. Systemic lupus erythematosus (SLE) is known as one of the autoimmune diseases complicated by C1-INH-HAE, and several cases have been reported [6, 12, 13, 15–17]. However, information on its clinical manifestations, disease course, and treatment is limited. This case report presents a patient with C1-INH-HAE who develops SLE with various clinical manifestations.

Case Presentation

A 31-year-old Japanese woman has a history of swelling of the lips without any specific triggers, which she began experiencing at age 14 years. At age 20 years, she was diagnosed with C1-INH-HAE based on blood test results showing low C4 and C1-INH activity. Her maternal grandmother and mother were also diagnosed with HAE. The patient has had episodes of skin and gastrointestinal angioedema several times per year, as well as one occurrence of laryngeal edema. For these episodes she was treated with plasma-derived C1-INH (Berinert [CSL Behring, Marburg, Germany]) at a hospital near her home.

At the age of 30 years, she developed malar rash, alopecia, and arthralgia in her hands and elbows. The arthralgia was considered to be arthritis associated with Sjögren's syndrome, which was suspected based on blood test results showing a high level of serum anti-Sjögren's-syndrome-related antigen A (anti-SS-A) antibody (>1200 U/mL; normal, <10 U/mL). She was prescribed prednisolone up to 10 mg/day.

At follow-up 8 months later, she reported general malaise. Her temperature was $>39^{\circ}\text{C}$. Physical examination showed oral ulcers and discoid rash on the anterior chest, and she admitted to the local hospital. On admission, laboratory test results were significant for the following elevated values: C-reactive protein (CRP), 5.65 mg/dL (normal, <0.20 mg/dL); aspartate transaminase (AST), 85 U/L (normal, <30 U/L); and alanine transaminase (ALT), 154 U/L (normal, <23 U/L). Results also showed leukopenia with a white blood cell (WBC) count of $1140/\mu\text{L}$ (neutrophils, $759/\mu\text{L}$) and thrombocytopenia with a platelet count of $9.7 \times 10^4/\mu\text{L}$. Antibiotics were started, but her symptoms did not improve. SLE was suspected based on the clinical symptoms, and an increased dose of prednisolone (20 mg/day) was initiated.

Four days later, she was transferred to our hospital for further diagnosis and specialized treatment. On physical examination, malar rash, oral ulcers, discoid rash, and arthralgia in her elbows and knees were observed (Fig. 1). Urinalysis showed proteinuria and occult blood. Laboratory data on admission are shown in Table 1 and are significant for CRP, 1.78 mg/dL; AST, 44 U/L; ALT, 25 U/L; WBC, $1720/\mu\text{L}$ (neutrophils, $1402/\mu\text{L}$); and platelet count, $16.8 \times 10^4/\mu\text{L}$. Compared with her previous treatment before the prednisolone was increased to 20 mg/day, her CRP and liver enzyme values had decreased, and leukopenia and thrombocytopenia had improved. Laboratory results also revealed elevated lactate dehydrogenase at 537 U/L (normal, 124–222 U/L) and ferritin at 622 ng/mL (normal, 6–138 ng/mL), in addition to hypocomplementemia with these values: complement C3, 111 mg/dL (normal, 68–144 mg/dL); complement C4, <2 mg/dL (normal, 12–33 mg/dL); and complement, total (CH50), <14.0 U/mL (normal, 30–46 U/mL). Assessment of autoantibodies was positive for antinuclear antibody (ANA) (1:80,

nucleolar pattern, speckled pattern), anti-ribonucleoprotein antibody (14.2 U/mL; normal, <10 U/mL), and anti-SS-A autoantibody (48,550 U/mL; normal, <10 U/mL). Anti-double-stranded-DNA antibody (immunoglobulin G) and anti-Smith antibody were negative. Bone marrow examination was performed to find the cause of cytopenia. Results showed no proliferation of blasts or tumor cells, but hemophagocytosis by macrophages was observed (Fig. 2). Computed tomography showed obvious splenomegaly. A thorough examination of the organ lesions revealed lupus retinopathy, and lupus nephritis class I according to the International Society of Nephrology/Renal Pathology Society classification was diagnosed (Fig. 3) [18]. Based on the findings of positive ANA, fever, nonscarring alopecia, oral ulcers, malar rash, discoid rash, arthralgia, leukopenia, thrombocytopenia, hypocomplementemia, lupus retinopathy, and nephritis, she was diagnosed with SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria [19].

Table 1
Laboratory data on admission.

Blood test							
WBC	1720	/μL	GOT	44	IU/L	β-D glucan	(-)
Blast	0.0	%	GPT	25	IU/L	Procalcitonin	(-)
Myelo	0.5	%	ALP	80	IU/L	HBs-Ag	(-)
Stab	0.0	%	LDH	537	IU/L	HBs-Ab	(-)
Seg	81.5	%	γ-GTP	29	IU/L	HBc-Ab	(-)
Eos	0.0	%	CPK	21	IU/L	HCV-Ab	(-)
Baso	0.0	%	Amylase	51	U/L	T-SPOT	(-)
Mono	4.5	%	TSH	1.05	μIU/mL	EBV-VCA-IgG	(+)
Lym	13.5	%	FT3	2.57	pg/mL	EBV-VCA-IgM	(-)
RBC	446	×10 ⁴ /μL	FT4	1.47	ng/dL	EBV-EA-IgG	(-)
Hb	12.2	g/dL	BNP	14.8	pg/mL	EBV-EA-IgM	(-)
Hct	35.3	%	Ferritin	622	ng/mL	EBNA-Ab	(+)
Plt	16.8	×10 ⁴ /μL	sIL-2R	855	U/mL	CMV-IgG	(+)
MCV	79.1	fL	IgA	570	mg/dL	CMV-IgM	(-)
MCH	27.4	pg	IgM	2894	mg/dL	CMV Ag (10, 11)	(-)
MCHC	34.6	%	IgG	87	mg/dL	Parvovirus B19-IgM	(-)
PT	121	%	C3	111	mg/dL		
PT-INR	0.93		C4	< 2	mg/dL		
APTT	26.4	sec	CH50	< 14	U/mL		
Fibrinogen	329	mg/dL	C1 inhibitor activity	< 25	%	Urinalysis	

sIL-2R soluble interleukin-2 receptor, *anti-ds-DNA Ab* anti-double-stranded-DNA antibody, *anti-RNP Ab* anti-ribonucleoprotein antibody, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *PR3-ANCA* serine proteinase3-anti-neutrophil cytoplasmic antibody, *CL-IgG* anti-cardiolipin immunoglobulin G, *CLβ2-GP1 Ab* anti-cardiolipin-beta2-glycoprotein I complex antibody, *PA-IgG* platelet-associated immunoglobulin G, *NAG* N-acetyl-beta-glucosaminidase, *FENa* fractional excretion of sodium

Blood test								
Lac	1.13	ratio	anti-nuclear Ab	1: 80		pH	7.5	
AT	86	%	(staining patterns)	nucleolar, speckled		Protein	(±)	
D-dimer	3.7	µg/mL	anti-ds-DNA Ab	(-)		Glucose	(-)	
CRP	1.78	mg/dL	anti-Smith Ab	(-)		RBC	(1+)	
TP	7.6	g/dL	anti-RNP Ab	(-)		WBC	(1+)	
Alb	3.2	g/dL	anti-SS-A Ab	(-)		NAG	15.5	U/L
BUN	6.1	mg/dL	anti-SS-B Ab	(-)		β2-microglobulin	3259	µg/L
Cre	0.37	mg/dL	MPO-ANCA	(-)		protein	0.21	g/gCr
Na	137	mEq/L	PR3-ANCA	(-)		Na	67	mmol/L
K	3.6	mEq/L	Direct Coombs	(+)		Cr	80	mg/dL
Cl	102	mEq/L	Indirect Coombs	(-)		FENa	0.22	%
Ca	8.1	mg/dL	anti-platelet Ab	(-)				
IP	2.7	mg/dL	CL-IgG	(-)	U/mL			
UA	3	mg/dL	CLβ2-GP1 Ab	< 0.7	U/mL			
Total-Bil	0.7	mg/dL	PA-IgG	42.7	ng/107c			
<i>sIL-2R</i> soluble interleukin-2 receptor, <i>anti-ds-DNA Ab</i> anti-double-stranded-DNA antibody, <i>anti-RNP Ab</i> anti-ribonucleoprotein antibody, <i>MPO-ANCA</i> myeloperoxidase-anti-neutrophil cytoplasmic antibody, <i>PR3-ANCA</i> serine proteinase3-anti-neutrophil cytoplasmic antibody, <i>CL-IgG</i> anti-cardiolipin immunoglobulin G, <i>CLβ2-GP1 Ab</i> anti-cardiolipin-beta2-glycoprotein I complex antibody, <i>PA-IgG</i> platelet-associated immunoglobulin G, <i>NAG</i> N-acetyl-beta-glucosaminidase, <i>FENa</i> fractional excretion of sodium								

After starting treatment with 20 mg/day prednisolone, the clinical symptoms tended to improve, so prednisolone was tapered with the concomitant use of 400 mg/day hydroxychloroquine and 1 mg/day

tacrolimus. After 4 weeks, her oral ulcers, malar rash, discoid rash, and arthralgia had disappeared and WBCs and platelets had increased (Fig. 4). Her splenomegaly had also improved (Fig. 5).

At a follow-up examination 7 months later, it was noted that the patient was able to maintain remission of SLE by continuing 7 mg/day prednisolone, 400 mg/day hydroxychloroquine, and 2 mg/day tacrolimus. However, her hypocomplementemia has persisted (C3, 113 mg/dL; C4, 4 mg/dL; CH50, 20.1 U/mL), which is thought to be associated with HAE. The patient continues to experience episodes of HAE several times per year, but the frequency of these episodes has not worsened since before she started treatment for SLE.

Discussion And Conclusions

The literature includes several reports of concomitant HAE and autoimmune diseases [6–17]. In 1986, Brickman et al. reported that 19 of 157 patients with C1-INH-HAE (12%) developed autoimmune diseases [6]; in 2011, Farkas et al. also reported that 15 of 130 patients with C1-INH-HAE (11.5%) had concomitant autoimmune diseases [11]. The estimated prevalence of autoimmune diseases in the general population is 4.5%, ranging from 2.7% in males to 6.4% in females [20], and patients with C1-INH-HAE may develop autoimmune diseases more frequently than the general population. Lupus is one of the most common autoimmune diseases in patients with C1-INH-HAE. In 2020, Levy et al. reviewed cases of concomitant C1-INH-HAE and autoimmune diseases [16]. Of 155 cases, lupus or lupus-like diseases accounted for 52 cases (34%) and SLE accounted for 30 cases (19%). Thus, it is important to note that autoimmune diseases, especially lupus, are concomitant with C1-INH-HAE.

This current case presentation reports SLE in a patient with C1-INH-HAE. The patient had a wide variety of clinical manifestations, including fever and mucocutaneous, joint, ocular, and renal lesions. Laboratory tests showed leukopenia, thrombocytopenia, hypocomplementemia, and immunologic abnormalities.

There are few reports on the patient characteristics and clinical manifestations in patients with C1-INH-HAE who develop SLE. In 2015, Sérézal et al. performed a literature review of 32 patients with C1-INH-HAE who developed lupus [15]. The median age at HAE onset was 14 years (3–30 years); the median age at lupus onset was 19.5 years (1–78 years). Of the 32 study patients, 15 (47%) had SLE, 6 (19%) had subacute lupus, 8 (25%) had discoid lupus, and 3 (9%) had lupus-like syndrome or an unspecified cutaneous lupus. Of the 15 patients diagnosed with SLE, 8 (53%) had mucocutaneous lesions, which a rate is higher than that reported in a European study (31.6%) [21]. These findings suggest that lupus associated with C1-INH-HAE has predominantly cutaneous symptoms. In addition, renal lesions were found in 8 patients in this study, but the detailed renal pathology was unknown. Little information is available about other organ involvement, the disease course, and treatment. In the current case, we were able to confirm multiple organ involvement, such as renal and ocular lesions, as a result of a thorough systemic examination. In addition, we were able to ascertain the detailed course of disease before and after the treatment.

The pathogenesis of C1-INH-HAE in patients who develop lupus remains unclear to date; however, a decrease in C4 and other early complement components may be associated with an increased risk for lupus [22]. One of the main functions of C1-INH is to regulate the complement pathway by preventing excessive activation of C4 and C2 through inhibition of the complement protease C1 in the classical pathway and mannose-binding lectin-associated serine protease 1/2 (MASP1/2) in the lectin pathway [23]. In contrast, the deficient function of C1-INH in HAE patients leads to autoactivation of C1, resulting in chronic activation and consumption of C4 and other early complement components.

The complement system plays a protective role in developing autoimmune diseases by contributing to clearance of immune complexes, clearance of apoptotic cells that may be the source of autoantigens, and tolerance to self-antigens [24–26]. Genetic deficiencies in C1, C4, and C2 are thought to increase the risk of developing the autoimmune diseases such as SLE and glomerulonephritis by lack of these protective mechanisms [26, 27]. Similarly, C1-INH-HAE has also been reported to be associated with SLE and glomerulonephritis [6–8, 12, 13, 15–17].

Although the mechanism for the development of autoimmune disease in patients with C1-INH-HAE remains controversial, a decrease in complement components, primarily C4, may affect immune regulation and clearance of immune complexes, predisposing these patients to develop autoimmune disease.

This case report presents a patient with C1-INH-HAE who develops SLE. She presented with a variety of symptoms, including fever and cytopenia in addition to mucocutaneous, joint, ocular, and renal lesions. The literature includes few reports on the clinical manifestations in and treatment of patients with both C1-INH-HAE and SLE, and more cases must be accumulated with detailed documentation of the clinical presentation and organ involvement, the disease course, and the treatment and outcomes.

Abbreviations

ANA = antinuclear antibody, anti-SS-A = anti-Sjögren's-syndrome-related antigen A, ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, C1-INH = C1 esterase inhibitor, HAE = hereditary angioedema, SLE = systemic lupus erythematosus, WBC = white blood cell.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

We obtained the patients' written consent prior for the purpose of publication of case details and images prior to submitting this article.

Availability of data and materials

The dataset supporting the conclusions of this article is available upon reasonable request.

Competing interests

The authors declared no conflicts of interest.

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Authors' contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. YU and RW wrote the manuscript. YU interpreted the case together with RW, TK, SN, HS, MK, TM, KS, RM, MM and HD. EI performed the histological examination of the kidney. MFMM and NK reviewed the manuscript for intellectual content. The authors read and approved the final manuscript.

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Figures

Figure 1

Cutaneous mucosal lesions before treatment: A) malar rash; B) oral ulcers; and C) discoid rash.

Figure 2

Bone marrow aspirate (May-Grunwald Giemsa stain, $\times 400$) shows hemophagocytosis by macrophages.

Figure 3

Renal biopsy. (A) Light microscopy: A-1) periodic acid-Schiff (PAS) stain; and A-2) periodic acid-methenamine-silver (PAM) stain. No mesangial proliferation, double contour of the glomerular basement membranes, or irregular spike formations are noted. (B) Immunofluorescence study shows deposition of immunoglobulin (Ig) A, IgM, and complement (C) 1q and C3c in glomeruli. (C) Electron microscopy: C-1) tubuloreticular inclusions (yellow arrow) were seen in some endothelial cells; and C-2) subepithelial electron-dense deposits (yellow circle) were observed.

Figure 4

Clinical course of treatment, symptoms, and laboratory data.

Figure 5

Computed tomography: A) on admission to the authors' hospital; and B) 3 weeks after treatment initiation. The patient had significant splenomegaly on admission, which improved after the treatment.