A case of episodic angioedema associated with eosinophilia

Takanori Shikiji, Yoshio Urano, Hirotsugu Takiwaki and Seiji Arase

Department of Dermatology, The University of Tokushima School of Medicine, Tokushima, Japan.

Abstract : *Background* Gleich et al. first described 4 cases of episodic angioedema associated with eosinophilia as a distinct entity in 1984. Since then, several cases of this disorder have been reported in the United States, Europe and Japan.

Observations **We report a case of a 22-year-old pregnant Japanese woman with this disorder. She had no fever and her general condition was good except the angioedema which was limited to her limbs. During an acute episode, her white blood cell count increased to 29,500/mm^3 with 50% eosinophils, following an elevated serum interleukin-5 (IL-5) level. Spontaneous resolution occurred in 1 month after the onset. In a 5 month follow-up, no evidence of cardiac or other visceral organ involvement was found, and no recurrence occurred.**

Conclusions **Our case, combined with those reported in the literature, suggests that Japanese cases of episodic angioedema associated with eosinophilia differ from Caucasian cases in clinical symptoms and some other points. J. Med. Invest. 44 : 103-108, 1997**

Key Word : *episodic angioedema, eosinophilia, interleukin-5*

INTRODUCTION

Episodic angioedema with eosinophilia was described by Gleich, et al. (1) as a distinct entity characterized by recurrent angioedema, urticaria, leukocytosis with remarkable eosinophilia, fever and periodically increased body weight. Since then several authors have also reported similar cases in Caucasoids (2-7). Most of the patients with this disorder had angioedema extending to the face and trunk as well as the extremities, with episodes recurring in all of them. Serum immunoglobulin levels were elevated in all Caucasian cases. Corticosteroid was administerd in most cases, which proved quite beneficial. Recently, 17 cases of this disorder have been reported in Japan (8-18). We presented an additional Japanese case along with a literary review of other cases. This study revealed some differences between Japanese and Caucasian patients.

CASE REPORT

A 22-year-old female, in her fifth month of pregnancy, presented with a 10-day history of continuous edema of the limbs. The ailment began with severe pruritus of the soles, followed by the non-pitting edema of the feet, lower legs, hands and forearms. She had no fever and her general condition was good.

Her family history did not include autoimmune, malignant, hematologic, or eosinophilic diseases. However, at the age of 12, she had uveitis which was not associated with blood eosinophilia, requiring treatment with prednisolone for the following 3 years.

On admission, a non-pitting, painless but pruritic edema, together with faint erythemas of various size and shape, were present on the bilateral lower legs and feet (Fig.1,A), and also on the bilateral forearms and hands (Fig.1,B) . The face and trunk were not affected, and none of the cervical, axillary or inguinal lymph nodes were palpable. Although she had gained 2 kg in weight over the previous 7 days, her urinary output was normal.

On admission, her white blood cell count was 17,000/mm^3 with 4% eosinophils. Serum IgG, IgA, IgM, and IgE levels were normal, with a radioallergosorbent test detecting no specific IgE antibodies against house dusts, mites, several molds, animal epithelia and feathers. Levels of circulating complements (C_3, C_4, total hemolytic

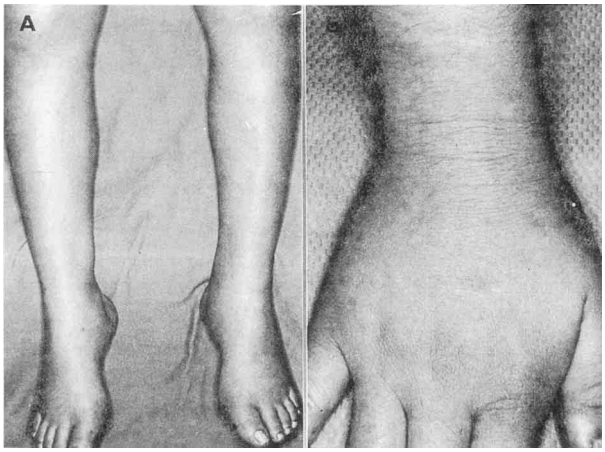

Fig.1. Angioedema with faint erythemas of the lower legs and feet (A), and the right hand (B)

Received for publication July 10, 1997 ; accepted July 31, 1997.

[1] Address correspondence and reprint requests to Takanori Shikiji, M.D., Department of Dermatology, The University of Tokushima School of Medicine, 3-18-15, Kuramoto-cho, Tokushima, Japan.

complement CH 50) and C_1-esterase inhibitor were within the normal range. Anti-nuclear antibody (ANA) was positive with a titer of 1 : 80 (speckled pattern), but other autoantibodies including anti-DNA, SS-A, SS-B, RNP and Sm were negative. The level of lactate dehydrogenase was elevated to 602 IU/L (normal, 237 to 454 IU/L). The results of the following tests performed during the episode were also negative or within normal range : urinalysis, stool tests for ova and parasites, red blood cell and platelet counts, liver and renal function tests, serum electrolyte concentration, C-reactive protein and plasma histamine levels. Electrocardiograms, echocardiograms, chest roentgengrams and abdomen ultrasoundgrams were all normal. Biopsy specimen taken from the dorsum of the foot (lacking in erythema) showed edema and a slight infiltration of eosinophils in the lower dermis and subcutaneous fat (Fig. 2). There was no evidence of vasculitis. A few mast cells were also seen in the lower dermis. WBC and eosinophil counts gradually increased, reaching 29,500/mm^3 with 50% eosinophils on day 10 (Fig 3). Bone marrow biopsy revealed an increased number of immature and mature eosinophils without evidence of leukemia.

No drugs were administerd because of her pregnancy and because of her good general condition. The angioedema improved gradually in parallel with a decrease in WBC and eosinophil counts. About 1 month after the onset, all skin symptoms disappeared completely but slight leukocytosis (11,100/mm^3) with eosinophilia (11%) was still noticed. Three months after the onset and 2 months before the expected date of delivery, she gave birth to a child without any abnormalities or eosinophilia.

We measured serum IL-5 levels during and after the episode by a sandwich enzyme-linked immunosorbent assay as described previously (19) (Fig. 3). The levels in 2 normal subjects (non-pregnant) were both less than 0.3 ng/ml. On day 4, about 1 week before the maximal blood eosinophilia, the level of the IL-5 was significantly higher than that of the normal controls. It decreased 3 months after the onset, though, it was still a little higher than the normal value.

DISCUSSION

This patient clinically demonstrated persistent angioedema on the limbs associated with blood leukocytosis and eosinophilia. Histological examination showed a slight infiltration of eosinophils in the lower dermis and subcutaneous fat. Eosinophilic leukemia and parasitic diseases were excluded in the clinical course and diagnostic examinations. Hypereosinophilic syndrome (HES) and Well's syndrome were important in the differential diagnosis. HES, in which cardiac and/or lung involvement is common, shows persistent eosinophilia with various skin manifestations including angioedema (20), and carries a poor prognosis (21). Transient eosinophilia and absence of visceral organ involvement in our patient were inconsistent with HES. Well's syndrome (22) is a disorder characterized by the existence of frame figure, histologically. This was not the case with our patient. Judging from the findings above, we diagnosed this case as episodic angioedema with eosinophilia.

A review of the literature has disclosed 28 cases reported as episodic angioedema with eosinophilia, covering 12 Caucasian and 16 Japanese cases (Table 1). We noticed that the Japanese cases differed from the Caucasian ones in some points. In the Caucasian cases, for instance, the male-to female ratio was 1 : 2. The angioedema was seen not only on their limbs but also on their faces and trunks. The patients usually demonstrated

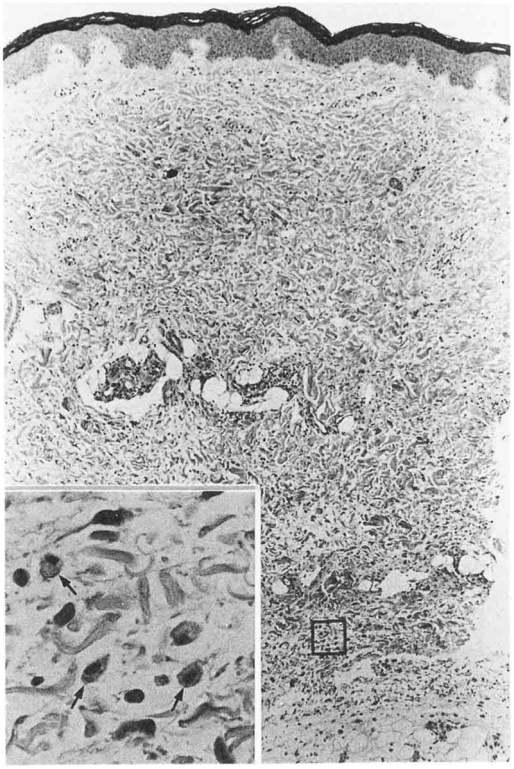

Fig. 2. Slight edema and infiltration of eosinophils mixed with lymphoid cells in the deep reticular dermis and subcutaneous fat. (hematoxylin-eosin, 13.2). Boxed area is seen at higher magnification (inset). Arrows show eosinophils. (hematoxylin-eosin, 132).

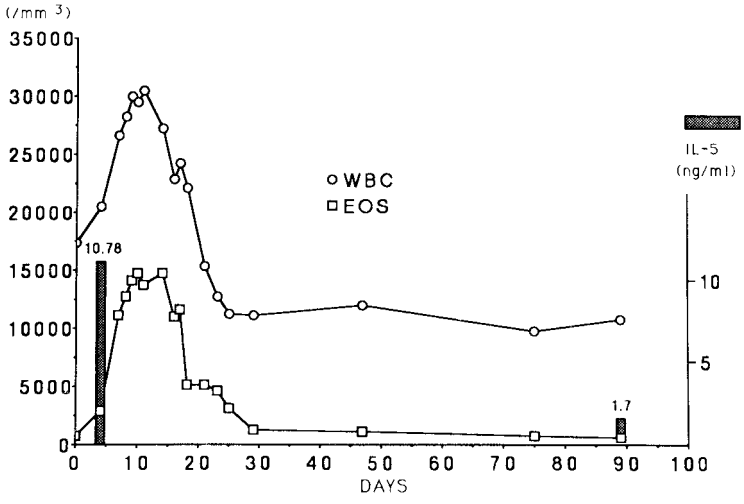

Fig. 3. Peripheral WBC and eosinophil counts and IL-5 levels during and after the episode. The value above the shaded bar indicates the IL-5 level.

Table 1. Literature review of episodic angioedema with eosinophilia #

A. Caucasic cases

Author	Age,y/ sex	Sites involved	WBC† (/mm³)	Eos† (%)	Abnormal laboratory findings	General symptoms	Durations	Treatment	Recurrence
Gleich et al.[1] 1984	16/M	Face, limbs	31,400	76	ALP ↑ IgG ↑ IgM ↑ TP ↑	ND	ND	Hydroxidine, cyproheptadine	(+) Monthly
	28/M	Limbs	108,000	88	IgM ↑	Fever	ND	Prednisone	(+)
	7/F	Systemic	60,000	60	IgM ↑ C 4 ↑	Fever	ND	Prednisone	(+) Every 4 to 6 weeks
	4/F	Face, limbs, trunk	45,000	67	IgM ↑ IgE ↑ platelet ↑ G-glob ↑	Fever	ND	Dexamethasone, prednisone	(+) Every 2 weeks
Katzen et al.[2] 1986	2.5/F	Face, limbs, trunk	52,000	62	IgM ↑ IgE ↑ helper Tac ↑	Fever	10days	Prednisone	(+) monthly
Wolf et al.[3] 1989	30/F	Systemic	31,000	75	IgM ↑ IgE ↑ helper Tac ↑	Fever, anuria	7-10 days	Busulfan and prednisone	(+) monthly
Schiavino et al.[4] 1990	24/F	Systemic	69,150	76	IgM ↑ IgE ↑ helper T ↑	Headache, dizziness	ND	Methylprednisone, betamethasone	(+)
Lassalle et al.[5] 1990	10/M	Face, legs pubes	16,400	76	immuno-complex ↑ IgM ↑	ND	10-15 days	ND	(+) monthly
	7/M	Face, extremities	12,000	39	IgM ↑ HLA-DR ↑ (blood mono-nuclear cell)	ND	3 days	(-)	(+) monthly
	25/F	Leg, fore-arm	9,200	59	IgM ↑	Asthnia	14 days	Betamethasone	(+) monthly
Butter-field et al.[6] 1992	19/F	Face, hands, feet,legs	57,900	84	IgM ↑ helper Tac ↑	Fever, vomiting	2 weeks	Prednisone, leucopheresis	(+) monthly
Putter-man et al.[7] 1993	18/F	Face, limbs	22,000	40	IgM ↑ IgE ↑ IL-1 ↑ sIL-2 R ↑	Fever, fatigue	4-6 days	Prednisone	(+) monthly

B. Japanese cases

Tsuru-machi et al.[8] 1990	22/F	Lower legs	33,330	78	LDH	(-)	About 1 month	Anti-histamine drugs	(-)
	37/F	Lower legs	9,400	38	LDH	(-)	About 1 month	Anti-histamine drugs	(-)
Tabe et al.[9] 1990	24/F	Limbs	21,000	71	LDH	(-)	ND	Anti-histamine drugs	(-)
Tsuda et al.[10] 1990	21/F	Limbs	19,300	62	(-)	(-)	About 1 month	(-)	(-)
Tsuda et al.[11] 1990	27/F	Feet	16,700	55	(-)	(-)	About 1 month	(-)	(-)
Yama-shita et al.[12] 1991	28/F*	Limbs	14,200	21	ND	ND	About 1 month	(-)	(-)
Ohashi et al.[13] 1992	24/F	Limbs	17,900	64	(-)	(-)	About 1 month	Anti-histamine drugs	(-)
	24/F	Limbs	8,600	41	(-)	(-)	About 1 month	Anti-histamine drugs	(-)
	24/F	Legs	8,200	48	(-)	(-)	About 1 month	Anti-histamine drugs	(-)
Nishimoto et al.[14] 1993	27/F	Hands, feet	44,600	91	ECP ↑	(-)	2.5 month	Anti-histamine drugs	(-)
Nishiiet al.[15] 1993	23/F	Limbs	16,000	62.3	ECP ↑	(-)	About 1 month	Anti-histamine drugs	(-)
Hara et al.[16] 1994	29/F	Limbs	19,000	31	ANA (+) ALP ↑ CH50 ↑	(-)	ND	Prednizone	(-)
	21/F	Legs, feet	12,000	70	LDH ↑ IgE ↑	(-)	ND	Prednizone	(-)
Okahara et al.[17] 1996	28/F	Legs, feet	15,100	69	ANA (+)	Fever	About 1 month	Anti-histamine drugs	(-)
	26/F	Legs	20,000	61	LDH ↑ IgE ↑	(-)	About 1 month	(-)	(-)
Kawano et al.[18] 1996	45/F	upper and lower limbs	23,000	57	CD69 (-) (peripheral eosinophils)	(-)	ND	Prednisone	(+)
Present case	22/F*	Limbs	29,500	50	LDH	(-)	About 1 month	(-)	(-)

WBC indicates white blood cell ; Eos, eosinophil ; ALP, alkaline phosphatase ; TP, total protein ; ND, no data reported ; G-glob, gammaglobulin ; Helper Tac, activated helper T cell ; Helper T, helper T cell ; LDH, lactate dehydrogenase ; IL-1, interleukin-1 ; sIL-2 R, soluble interleukin-2 receptor ; ECP, eosinophil cationic protein ; ANA, anti nuclear antigen

* A pregnant case

† A maximum value was represented.

monthly episodes of angioedema and eosinophilia accompanied by systemic symptoms such as fever and malaise. Various types of immunological abnormalities, including increased serum IgM (1-7) and IgE (1-4, 7) levels and elevated levels of circulating activated T-helper cells, were commonly found among these cases (2-4, 6). The patients required systemic corticosteroid therapy at each episode. However, Japanese patients were all young females in their twenties, except for 2 cases. The angioedema was limited to their limbs and did not extend over their faces and trunks. In contrast with the Caucasian cases, most of the patients had no fever or malaise during the episode, and their symptoms resolved spontaneously or with antihistamines in about 1 month. Moreover, they experienced no recurrence of the disorder. The cause of the difference between the two groups remains to be answered.

The patient described here was pregnant. Various types of specific dermatoses may occur during pregnancy, including pruritus, prurigo, papule, erythema and herpes (23). However, angioedema is not common in pregnancy. In the literature, we found 1 Japanese case with this disorder associated with pregnancy (12), but possible correlations between the angioedema and pregnancy remain unclear.

IL-5 possesses a wide variety of biological activities including the induction of eosinophil differentiation and proliferation. Butterfield et al. (6) demonstrated that, in the patients with this disorder, IL-5 levels peaked several days before maximal eosinophilia. From our patient, we have obtained results consistent with such findings. These observations suggest that IL-5 plays an important role in eosinophilia in episodic angioedema with eosinophilia.

ACKNOWLEDGMENTS

We wish to thank Dr. N. Tsuruoka (Suntory Institution for Biomedical Research, Osaka, Japan) for providing monoclonal and polyclonal antibodies to recombinant human interleukin-5.

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