

Eleven Cases of Angioedema with Eosinophilia Treated in a Single Hospital in Japan

Shinichiro Nakachi¹ and Shigeko Inokuma¹

ABSTRACT

Background: Angioedema with eosinophilia (AE) is mostly reported in Japanese patients, and only as case reports. In this study, we aimed to determine how prevalent AE cases appear, the characteristic features and the course of AE, and to evaluate whether corticosteroid therapy for AE is necessary or not.

Methods: The patients whose blood samples showed an eosinophil count of $\geq 2,000/\mu\text{L}$, among the samples tested for blood cell counts and differential counts between January 2006 and December 2010, in Japanese Red Cross Medical Center, were firstly included. Among these, patients with AE were extracted.

Results: All of the 11 patients were Japanese young females. One patient with arthralgia showed radioisotope accumulation in the joints by bone scintigraphy. The peak peripheral blood eosinophil count was $7,839 \pm 6,008$ ($2,130$ – $23,170$)/ μL after visiting our hospital. An increase in white blood cell count was only due to an increase in eosinophil count. Serum C-reactive protein and IgE levels remained almost normal. Peripheral blood eosinophil count decreased steadily for 8 weeks, regardless of corticosteroid use. Edema in all of the patients and arthralgia in 6 patients improved within 12 weeks. As far as followed, none of the patients had a recurrence of AE.

Conclusions: AE developed in Japanese young females and likely showed a single course. In AE, the count of eosinophil of $10^4/\mu\text{L}$ was observed. Only eosinophil count increased among leukocyte series. Serum C-reactive protein and IgE levels remained almost normal. The eosinophil count in AE patients will return to the normal level within 8 weeks even without corticosteroid therapy.

KEY WORDS

angioedema, arthritis, corticosteroid, eosinophilia, nonepisodic

INTRODUCTION

Episodic angioedema with eosinophilia (EAE) was first reported in 1984 by Gleich *et al.*¹ This was characterized by peripheral blood eosinophilia, elevated serum IgM level, fever, urticaria, weight gain, angioedema, and absence of involvement of internal organs. After that, several case reports of angioedema with eosinophilia (AE) were published.^{2–12}

In 1998, Chikama *et al.* reported the cases of transient variant EAE in Japan, which was proposed as nonepisodic angioedema with eosinophilia (NEAE).¹³ Almost all the reported AE cases in Japan and Korea were nonepisodic.^{14–19} These NEAE cases involved mostly young females, whose features were edema localized in the hands and feet, arthralgia, eosinophilia, normal immunoglobulin levels, and lack of in-

ternal organ involvement.^{14–19} Some of the NEAE cases remitted spontaneously within a few months and had only a single attack. However, despite the possibility of spontaneous remission, lack of information about the clinical characteristics and the course of AE sometimes results in the tendency to administer corticosteroid owing to a surprisingly high peripheral blood eosinophil count and marked symptoms. No report has been available on a larger number of AE cases more than 10 in a single hospital. There has also been no report showing the prevalence of AE, or clearly showing no need for corticosteroids, so far. We have treated 11 AE patients in our hospital. Thus, we retrospectively evaluated our patients with AE to determine how prevalently it appeared, characteristics, and clinical courses of AE including the therapies for AE and their outcomes and to determine

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Table 1 Clinical and laboratory features of angiodema with eosiphilia patients

Patient	Age/ sex	Cilnical symptoms				Laboratory data									Steroid therapy
		Fever	Weight gain (kg)	Arthral- gia	Dura- tion of symp- toms (weeks)	WBCs (/μL)	Eosino- phil (/μL)	Neutro- phil (/μL)	IgG (g/L)	IgA (g/L)	IgM (g/L)	IgE (IU/mL)	CRP (mg/L)	ESR (mm/ h)	
1	24/F	-	NA	-	2	29,100	23,170	2,840	10.77	1.28	1.97	48	1.1	ND	-
2	24/F	-	NA	+	3	22,500	14,440	5,010	10.72	3.22	0.70	49	0.8	7	-
3	28/F	-	NA	+	4	14,400	9,430	2,980	9.50	1.27	1.57	97	0.5	4	-
4	37/F	-	5	+	4	15,300	8,640	4,310	14.28	1.46	1.84	81	1.0	8	-
5	28/F	-	NA	-	2	15,200	8,170	3,760	13.68	1.66	1.63	359	0.3	ND	-
6	34/F	-	NA	+	8	14,800	6,900	6,130	13.69	1.62	0.75	189	0.8	ND	+ [†]
7	38/F	-	1	+	12	9,200	3,700	2,960	9.53	1.12	1.93	46	0.3	2	+ [†]
8	24/F	-	NA	-	5	11,800	3,520	6,040	10.91	1.53	2.05	21	0.1	ND	-
9	29/F	-	NA	-	6	10,200	3,470	4,230	11.68	2.20	ND	ND	0.4	ND	-
10	23/F	-	1	+	4	9,100	2,660	4,460	9.90	1.32	1.08	18	23.4	7	-
11	24/F	-	NA	-	8	12,500	2,130	8,550	ND	ND	ND	ND	0.3	ND	+ [‡]

NA, Not available; ND, Not determined; F, female; WBCs, White blood cells; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate.

[†] Transient use.

[‡] Continued use.

whether corticosteroid treatment of AE is necessary or not.

METHODS

The patients, who visited Japanese Red Cross Medical Center, and whose blood samples were measured for blood cell counts and differential counts, and showed an eosinophil count of $\geq 2,000/\mu\text{L}$, between January 2006 and December 2010, were firstly included. Among these, patients with AE were extracted. AE was diagnosed by doctors in charge, mainly on the basis of angioedema on distal extremities that developed concurrently with peripheral eosinophilia and improved in parallel with a decrease in eosinophil count. The patients' medical charts were reviewed for sex, age, past history of any allergies, and any episodes of something as such infection before the development of edema. Fever, body weight gain, symptoms other than edema including arthralgia or arthritis, and internal organ involvement were also examined. The durations of symptoms and eosinophilia, corticosteroid dose, and treatment outcomes were also checked. The clinical charts were reviewed until their last visits. Laboratory test parameters examined included white blood cell (WBC), eosinophil, and WBC other than eosinophil counts, serum IgG, IgA, IgM, and IgE levels, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR). A whole body bone scintigraphy with $^{99\text{m}}\text{Tc}$ methylene diphosphonate was performed to evaluate arthritis. Exclusion criteria were preexisting underlying diseases other than allergies, pre-use of corticosteroid for diseases other than AE. Whether the pa-

tients had a recurrence of AE or not, afterwards, was studied by means of making calls to them. As this study was retrospective chart-oriented study, informed consent was taken from all of the patients we could reach. The study design was approved by the ethical committee of our hospital.

RESULTS

During the study period, 474,538 blood samples over the age of 20 were examined for the differential count of WBCs. Among them, 600 samples from 223 patients showed an eosinophil count of $\geq 2,000/\mu\text{L}$. Eleven patients out of the 223 were diagnosed as having AE.

All of them were Japanese females, aged 28.5 ± 5.3 (range: 23-38). The duration of edema was 5.2 ± 2.8 (range: 2-12) weeks. The follow-up period was 5.8-7.0 (range: 1-23) months. 8 out of 11 patients could have had a contact by phone; all of them had no recurrence of AE after their last visit to date, for 19.9 ± 15.0 (range: 1-49) months.

Clinical symptoms and laboratory data are listed in Table 1. None of the patients had any other preexisting or concurrently developing underlying disease including infectious diseases, malignancies, and collagen diseases other than allergies. One patient had atopic dermatitis, and another had aspirin allergy. No internal organ involvement was observed in any patients. An increase in body weight of up to 5 kg was documented in four patients. Edema was observed in distal extremities symmetrically, mostly in the hands and feet, and severe around the joints. As for the articular symptom, 6 patients had it symmetrically in

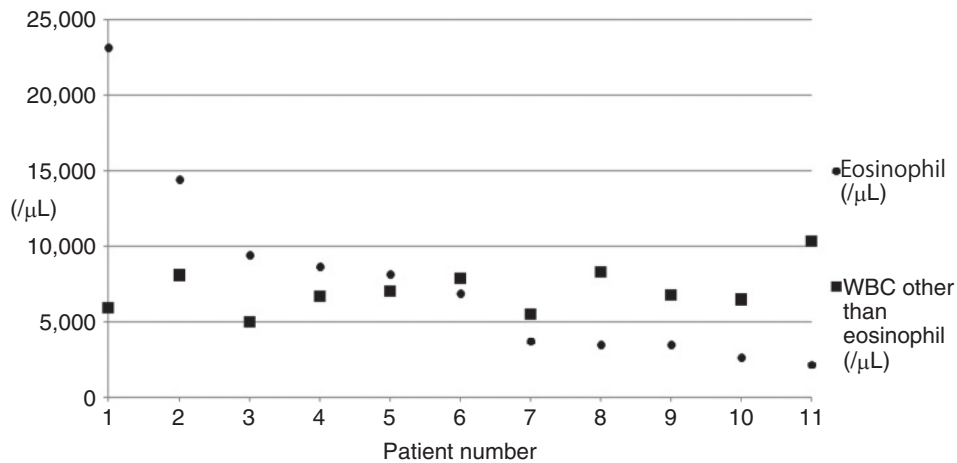


Fig. 1 Peripheral blood WBC and eosinophil counts in AE patients. Patients 6 and 7 were transiently administered a low dose of a corticosteroid. Patient 11 had had tapering dose of a corticosteroid.

several joints; 2 of them underwent bone scintigraphy. One of them showed active radioisotope accumulation in the joints. The other patient, who already showed improvement of the articular symptom when tested, showed no radioisotope accumulation.

The peak peripheral blood eosinophil count in our hospital was $7,839 \pm 6,008$ (2,130-23,170)/ μL . The serum IgE (101 ± 104 IU/mL), IgG (11.47 ± 1.71 g/L), IgA (1.67 ± 0.59 g/L), and IgM (1.50 ± 0.50 g/L) levels were normal. Serum CRP level was within normal limits with the exception of one patient who had arthritis with active radioisotope accumulation. Serum lactate dehydrogenase (LDH) level slightly increased (266 ± 36 IU/L, normal range: 118-240 IU/L).

An increase in WBC count was only due to an increase in eosinophil count (Fig. 1), that is, the count of leukocytes except for eosinophils including neutrophils, basophils, monocytes, and lymphocytes, did not change throughout the course of eosinophil increase and decrease in each patient except for Patient 11. Patient 11 was administered a sustained corticosteroid, who showed a decreasing eosinophil count and an increased neutrophil count, which are indicative of corticosteroid use.

The courses of decrease in peripheral blood eosinophil counts are shown in Figure 2. Peripheral blood eosinophil count decreased steadily for 6 weeks after the first visit.

Regarding prednisolone therapy, Patient 6 had only 3 mg/day for 3 days, Patient 7 had 5 mg/day for 10 days, and Patient 11 had 20 mg/day for 4 days which was tapered to 0 mg in 16 days, before visiting our hospital. None of the patients had additional corticosteroids in our hospital. Anthelmintic was not administered to any patients. Edema in all of the patients and arthralgia in 6 patients improved within 2 months; the most rapid improvement was observed

in 2 weeks. As shown in Figure 2b, the declining courses of eosinophil count did not differ between patients with or without corticosteroid. The lineal declining manner in logarithmic scale sustained for up to 6 weeks. The changing courses in patients with corticosteroid were similar to those in 8 patients without it. Although the changing course in another patient was not available, the symptom courses of these 3 patients did not differ especially from other patients.

DISCUSSION

As far as we searched the English literature, almost all clinical reports on AE were case reports and no study including ≥ 10 cases in a single hospital has been reported. The prevalence of AE has not yet been determined. Although many of the reported cases required no corticosteroid treatment, the time course of eosinophil count was not described.

We tried to elucidate how prevalent AE were appeared in our hospital. 0.1% of the total samples tested showed eosinophil count of $\geq 2,000/\mu\text{L}$. Among all of the 223 patients with an eosinophil count of $\geq 2,000/\mu\text{L}$, 11 (4.9%) had AE. Among eosinophilia patients with a count of $\geq 5,000/\mu\text{L}$, 6/41 (14.6%) had AE, and among those with a count of $\geq 10,000/\mu\text{L}$, 2/18 (11.1%) had AE. This indicates that AE is actually a relatively common disease among patients with eosinophilia, particularly among patients with a much higher count. We have treated more than 10 AE patients during 3 years in our ordinary general hospital with specialists in allergology. It appears that if AE is widely known, much more cases of AE would be detected at least in Japan.

The mean eosinophil count in AE patients was as high as 7,839/ μL , and 2 patients showed a maximum count of $\geq 10,000/\mu\text{L}$. This indicates that the eosino-

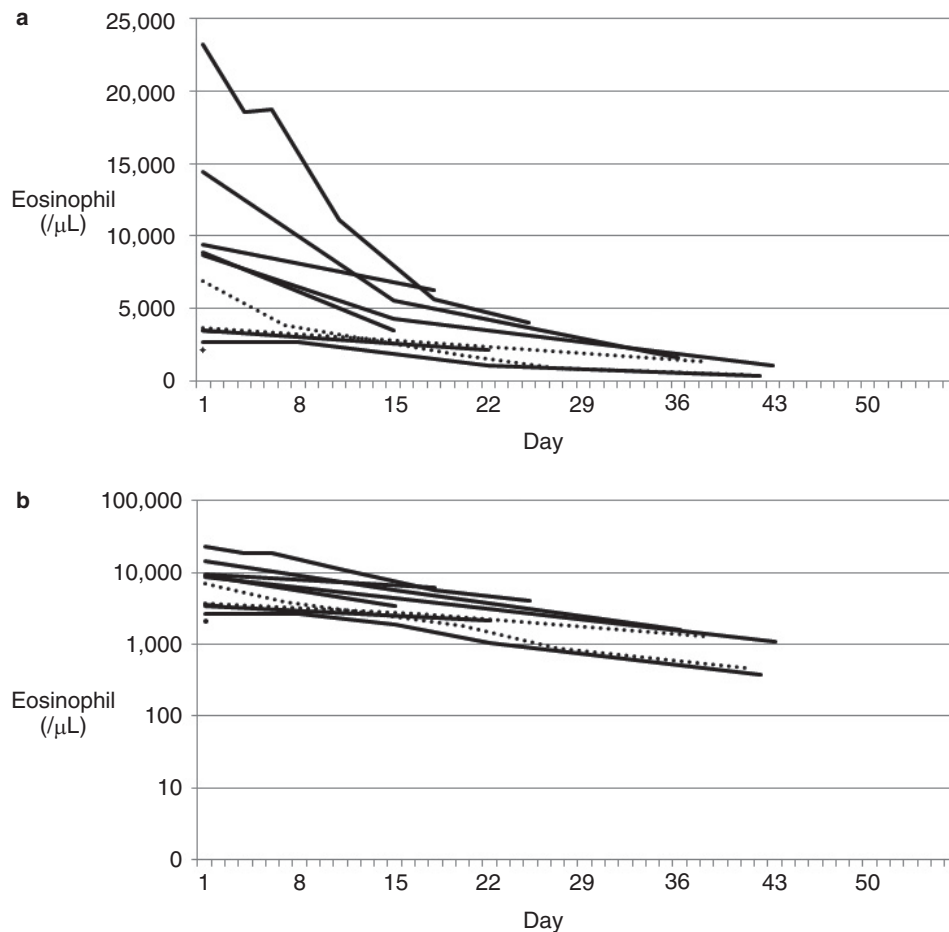


Fig. 2 Changes in peripheral blood eosinophil count. Patients 6, 7, and 11 shown as dotline had corticosteroid treatment before visiting our hospital. (a) In real number. (b) In logarithmic number.

phil count in AE patients is comparatively higher than that in other diseases with eosinophilia such as atopic diseases, in which the count is usually only mildly increased. Despite such a high eosinophil count, AE has no serious internal organ involvement. Regarding serum IgE level, all of our patients except one showed levels within the normal range, and none of the patients showed a markedly high level. Concerning inflammatory markers, CRP level did not increase except for one patient who had arthritis, and ESR was not elevated in all of the patients. Serum IgM level was within normal range in our patients, although a high level was reported by Gleich *et al.* as a characteristic feature of EAE.¹

All of the AE patients in our hospital were Japanese young women, had edema localized in distal extremities, and had a slight weight gain; these features were quite similar to those in many case reports from Japan.³⁻¹⁸ Although arthritis complicated by AE was described in many reports,^{6,14,16-19} no confirmed diagnosis was made. We conducted bone scintigraphy on 2

patients, and observed radioisotope accumulation in the joints in one in the active phase of arthralgia that developed concurrently with eosinophilia. In another patient, a scarce accumulation was observed when examined after arthralgia subsided with a decreased eosinophil count. A bone scintigraphy image showed that arthritis could have actually taken place at least in some patient in the active phase of AE.

Not only the pathogenesis, but preexisting status of AE has been so far unclear. One case of AE after an infection was reported.²⁰ However, our patients did not have any preexisting status or preceding events such as an allergic attack or an infection.

None of our patients have revisited our hospital after their follow-up period and there has been no request for patients' information from other hospitals concerning the recurrence of AE in these patients to date. AE did not recur in all of our patients during the follow-up period of 3 to 30 months. This observation is consistent with that in many reports, i.e., AE in Japanese patients is generally nonepisodic.¹³⁻¹⁸ Jang

et al. reported that AE in Korean patients was also nonepisodic and involved young women.¹⁹ Although it is difficult to confirm whether AE is nonepisodic or episodic, most cases of AE in Japanese and also Korean patients are considered to be nonepisodic, at least as far as the reports' follow-up periods covered.¹³⁻¹⁹

A corticosteroid is sometimes administered to patients with AE more likely owing to a substantial elevation of peripheral blood eosinophil count, rather than owing to patients' complaints or the physical finding of edema. However, most AE patients might have attained a complete remission without corticosteroid treatment, as was obtained in most of our patients, with and without corticosteroid treatment. The decrease in eosinophil count tended to be linear in a logarithmic scale, and almost the same with or without corticosteroid treatment.

In a case in which the AE patient is a young Japanese female, presents with angioedema in the distal extremities, shows an increased peripheral blood eosinophil count, and shows neither serum IgE level elevation nor positive inflammatory markers, corticosteroids should not be administered to such a patient. Edema and other symptoms will disappear in several weeks. Among diseases complicated by eosinophilia, AE is rather much more prevalent, particularly among cases with an eosinophil count of $\geq 5,000/\mu\text{L}$.

When predicting the course of decrease in eosinophil count, the count might return to the normal level within eight weeks, as supposed from the logarithmic graph in Figure 2b.

In conclusion, AE developed in Japanese females, and likely showed a single course. In AE, an eosinophil count of $10^4/\mu\text{L}$ was observed. Only eosinophil count increased without an increase in the count of other leukocyte series. Serum CRP and IgE levels stayed almost normal. Arthritis associated AE was confirmed by scintigraphy. Eight patients out of the 11 did not require corticosteroid treatment. Eosinophil count returned to normal levels within eight weeks. All the patients had no recurrence of AE.

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