CASE REPORT

Nonepisodic angioedema with eosinophilia with remarkably high blood eosinophil counts

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INTRODUCTION

Angioedema with eosinophilia (AE) is a rare idiopathic angioedema that predominantly affects young women. AE is classified into the following 2 variants: episodic angioedema with eosinophilia (EAE) and nonepisodic angioedema with eosinophilia (NEAE). These 2 variants have some similar clinical features, such as angioedema with a predominantly peripheral distribution, eosinophilia, weight gain, and benign prognosis without internal organ involvement.1,2 However, there are some crucial differences between the 2 variants. Epidemiologically, while EAE has been reported mainly in western countries, NEAE occurs commonly among young women in East Asian countries such as Japan and Korea.1,2 Clinically, EAE is characterized by recurrent episodes of angioedema and elevated serum immunoglobulin (Ig) M, whereas patients with NEAE usually experience only a single episode of angioedema with normal IgM levels.1,2 We herein present a Japanese female patient with NEAE who had a remarkably high blood eosinophil count. In such case, it is important to rule out other diseases associated with eosinophilia such as hypereosinophilic syndrome and to make a correct diagnosis of NEAE. In addition, we also discussed possible contributing factor to the tremendously high absolute eosinophil count (AEC).

CASE REPORT

A 37-year-old Japanese woman visited a dermatology clinic because of a 3-week history of edema in the extremities that resulted in weight gain of 5 kg (day 20 in Fig 1). The edema around the knees was accompanied by arthralgia. She had no personal or family history of hereditary angioedema or any allergic diseases. There was no medication started just prior to the edema, although she had been taking oral lithium carbonate, lorazepam, and zolpidem tartrate for 5 years to treat bipolar disorder. Laboratory tests showed elevated leukocyte count (10,600/μL). AEC was not examined. Ten days after initiation of an oral antihistamine, which was not effective, she was referred to the department of general medicine in our hospital (day 30 in Fig 1).

She did not have fever, urticaria, or evidence of parasitic infection. Her weight had slightly decreased over the prior 10 days; however, hematological tests demonstrated a tremendously elevated AEC (35,780/μL), which accounted for 88% of total white blood cells (40,660/μL) (Fig 1). The level of lactate dehydrogenase was also elevated (409 U/L). Erythrocyte

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Abbreviations used:
AE: angioedema with eosinophilia
AEC: absolute eosinophil count
EAE: episodic angioedema with eosinophilia
G-CSF: granulocyte-colony stimulating factor
IL: interleukin
Ig: immunoglobulin
NEAE: nonepisodic angioedema with eosinophilia

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sedimentation rate, C-reactive protein, and serum IgM levels were all within the normal range (Table I). No specific findings were observed in electrocardiogram, serum vitamin B12, troponin C, and serological tests of liver, kidney, thyroid gland, and adrenal gland function (data not shown). Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factor were negative (data not shown). Taken together, the general physician excluded hypereosinophilic syndrome because there was no organ damage, association with neoplasm, parasitic infection, or allergic diseases. Then, being suspected NEAE, she was referred to our department for further examination and treatment (day 38 in Fig 1). Physical examination revealed that symmetrical nonpitting edema in the lower extremities remained conspicuous (Fig 2, A). A skin biopsy specimen obtained from the right lower leg revealed mild dermal edema and conspicuous eosinophil infiltration around blood vessels and appendages in the dermis and in the subcutaneous adipose tissue (Fig 3, A and B). While antihistamines and topical corticosteroids were not effective, a moderate dose of prednisolone (0.5 mg/kg/day) dramatically decreased the angioedema in a week (Table I and Fig 2, B) with a rapid and drastic decrease in body weight, white blood cell count (5680/μL), and AEC (80/μL) to normal levels (Table I, day 45 in Fig 1). After the oral corticosteroid was gradually tapered off over 4 weeks, there had been no recurrent episodes of angioedema for 2 years.

**DISCUSSION**

Eosinophilia occurs in a wide variety of diseases, including hypereosinophilic syndrome, parasitic infection, drug-induced angioedema, and AE.3 In this case, hypereosinophilic syndrome was ruled out due to the lack of internal organ involvement. There was no evidence of parasitic infection on physical examination. The lack of changes in medications prior to disease initiation excluded drug-induced angioedema. In addition, she had only a single episode involving typical symptoms of AE such as angioedema in the extremities and weight gain with a normal serum IgM level. Thus, we made a diagnosis of NEAE. Regarding treatment for NEAE, there have been some reported cases of spontaneous remission or successfully treated with antihistamines in a few weeks.4,5 However, systemic corticosteroids have sometimes been administered, more likely due to substantial elevations in AEC rather than clinical symptoms such as edema.6,7 In the present case, as in previously reported cases, we used systemic corticosteroids because of the not only edema with arthralgia refractory to antihistamines but also extremely elevated AEC.

In most Japanese and Korean patients with NEAE, AEC has been reported to be 1000 to 20,000/μL.2,3,5-8 Nakachi and Inokuma6 demonstrated that the mean eosinophil count in 11 Japanese patients with NEAE was 7839/μL. However, our patient had extremely high eosinophilia (35,780/μL). Although the pathogenesis of eosinophilia in NEAE has not been fully elucidated, there have been some reported cases of NEAE with elevated serum levels of interleukin (IL)-5.3,9 Mizukawa et al9 reported that serum G-CSF levels were elevated in 2 of 3 patients with NEAE, and G-CSF and IL-5 are known to enhance eosinophil survival and capillary leakage. Although serum
G-CSF and IL-5 were not examined in this patient, we speculated that oral lithium carbonate possibly contributed to substantial eosinophilia by increasing serum G-CSF level. In addition, increase of AEC occurred 10 days later than body weight gain (Fig 1). Tanaka et al reported similar cases in which the peak AEC occurred 7 to 10 days after peak body weight gain in a Japanese literature. These findings suggest that some patients with NEAE may present only angioedema, without eosinophilia, in their early phase of the disease course. Therefore, when we see a patient suffering from angioedema without eosinophilia, AEC should be checked again in 7 to 10 days to avoid missing early-stage NEAE.

**Fig 2.** Clinical features of nonepisodic angioedema with eosinophilia. Symmetrical non-pitting edema of (A) the knees and (B) the lower legs and feet. After 1 week of systemic corticosteroid therapy, there was a dramatic decrease in edema of (C) the knees and (D) the lower legs and feet.

**Fig 3.** Histological findings of nonepisodic angioedema with eosinophilia. A, Infiltration of inflammatory cells throughout the entire dermis. B, Conspicuous eosinophil infiltration around blood vessels and appendages. Hematoxylin eosin staining, original magnification (A) × 40; (B) × 200.
Conflicts of interest
None disclosed.

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