Four Japanese Cases of Episodic Angioedema with Eosinophilia
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Here we describe four young Japanese women aged 25–33 years, whose clinical findings are characterized by episodic angioedema, marked leukocytosis with eosinophilia, benign course with spontaneous remission or low-dose prednisolone treatment. The recognized causes of eosinophilia, such as allergy, parasite, and collagen diseases, and the causes of edema, such as heart, kidney, and liver diseases, were ruled out. The findings in these patients are very similar to those reported as episodic angioedema with eosinophilia, which is clearly distinct from the so-called hypereosinophilic syndrome. We suggest that this syndrome is not rare, and should be widely recognized as a new clinical entity for accurate and prompt diagnosis.

Key words: hypereosinophilic syndrome, major basic protein

Introduction

Angioedema can be classified as IgE-dependent, complement-mediated, or idiopathic (1). Hypersensitivity to specific antigens and physical stimuli such as cold implies an IgE mechanism. Angioedema also occurs in C1 inhibitor deficiency with an autosomal dominant inheritance or in necrotizing angiitis, which is thought to be an immune-complex disease with hypocomplementemia. None of these disorders are associated with eosinophilia.

In 1984 Gleich et al (2) described four patients with recurrent attacks of angioedema with marked eosinophilia, and suggested that the syndrome was a new clinical entity distinct from the so-called hypereosinophilic syndrome (3, 4). Here we describe four Japanese young women whose clinical features are very similar to those observed in episodic angioedema associated with eosinophilia.

Case Reports

Case 1

A 25-year-old Japanese woman was admitted to the Department of Internal Medicine of Tokyo Kohsei-Nenkin Hospital, Tokyo, Japan, for the evaluation of leukocytosis with eosinophilia in 1989 (Fig. 1). She had been well until four weeks before, when she began to have pruritis on the bilateral ankles without any eruption. One week later she noticed edema on her feet, which persisted for about three weeks. The blood test at another hospital revealed that the white cell count was 16,300/mm³ with 36.7% eosinophils, and she was referred to our hospital. The physical examination revealed pitting edema on bilateral feet and lower extremities and heat and swelling of bilateral knee joints. The white cell count was 23,200/mm³ with 40.0% eosinophils. Serum albumin was 4.7 g/dl, BUN 11.5 mg/dl, and creatinine 0.81 mg/dl. Serum aspartate aminotransferase and alanine aminotransferase were within normal limits. She was admitted one week later on October 28, 1989.

She had an episode of bronchial asthma at the age of 2 with no recurrent attacks thereafter, and occasional episodes of allergic rhinitis from February to April every year since the age of 15. The family history was negative for hereditary angioedema, autoimmune, or eosinophilic diseases.

The physical examination on admission revealed that the edema had already almost disappeared and no other abnormality was found. The white cell count was reduced to 7,400/mm³ with 40.0% eosinophils. The red blood cell count was 432 x 10⁴/mm³, hemoglobin 11.9 g/dl, and platelet count 22.1 x 10⁴/mm³. Repeated urinalyses revealed no abnormalities. Cardiac disease was ruled out based on the normal findings by chest roentgenogram, electrocardiogram, and echocardiogram.

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Bone marrow aspiration from the sternum showed 11.2 $\times 10^9$/mm$^3$ of nucleated cells with 38.8% eosinophils, almost all of which appeared normal and mature under light microscopy. Chromosomal analysis revealed a normal karyotype. Serum immunoglobulin (Ig) E, IgA, IgG, IgM, serum complement 3 (C3), and C4 levels were within normal limits (Table 1). Serum C-reactive protein (CRP) was 0.5 mg/dl (normal, <0.8) and erythrocyte sedimentation rate (ESR) was 3 mm/h. Multiple stool samples were negative for ova and parasites. Serum IgG, IgM, IgE, C3, C4, and CH50 were all within normal limits (Table 1).

After admission, the edema was resolved without any medication, and the white cell count and the eosinophil count decreased to 6,200/mm$^3$ and 9.0%, respectively, at discharge on October 6, 1984. No recurrent attack has been observed since then.

Case 2

A 28-year-old Japanese woman was admitted to our hospital on September 22, 1984, because of marked edema, body weight gain of 2.5 kg, a slight fever of 37°C, and mild eosinophilia. The edema did not improve in spite of the administration of diuretics. The past history and the family history were negative for allergies or any other notable disease.

The laboratory findings are summarized in Table 1. The white cell count on admission was 8,100/mm$^3$ with 24% eosinophils. Multiple stool samples were negative for ova and parasites. Serum IgG, IgM, IgE, C3, C4, and CH50 were all within normal limits (Table 1).

After admission, the edema was resolved without any medication, and the white cell count and the eosinophil count decreased to 6,200/mm$^3$ and 9.0%, respectively, at discharge on October 6, 1984. No recurrent attack has been observed since then.

Case 3

A 33-year-old Japanese woman was seen at our hospital for edema (Fig. 2A) and body weight gain of 1-2 kg on November 8, 1989. She was given furosemide 20 mg daily for 5 days with no improvement of the edema. As shown in Table 1, the white cell count was 9,800/mm$^3$ with 9.0% eosinophils. The medical record revealed that the white cell count had been 5,400/mm$^3$ with 3.0% eosinophils 10 years earlier. Serum IgE, CH50, C3, C4, and C4 inhibitor were within normal limits (Table 1).

Administration of prednisolone (10 mg daily) was started on November 22. The edema was markedly decreased on November 27, and completely disappeared on December 8, when the white cell count was reduced to 6,100/mm$^3$ with 1.4% eosinophils (Fig. 2B). Accordingly, the dose of prednisolone was reduced to 5 mg daily. There has been no sign of a recurrent attack since December 12, 1990, when prednisolone was discontinued.

Case 4

A 25-year-old Japanese woman was examined at our hospital in 1989 for pain in bilateral knee and elbow joints and edema on the lower extremities. She had been well until several weeks before, when she began to have
pain in bilateral knee joints especially when squatting. One week later she noticed swelling of the ankles. She was first seen at the Department of Orthopedic Surgery of our hospital, where the blood test revealed that the white cell count was 14,300/mm³ with 15.0% eosinophils. CRP was 3.4 mg/dl and ESR was 5 mm/h. She was referred to the Department of Internal Medicine, where the physical examination revealed no abnormality except for the edema on bilateral lower extremities and the swelling and pain of the knee and elbow joints. The laboratory findings are summarized in Table 1.

Prednisolone (20 mg daily) was started on October 23. The edema decreased on October 25, and the dose of prednisolone was reduced to 15 mg daily. On October 30 the edema and the joint pain disappeared completely, when the white cell count was 14,800/mm³ with 5.0% eosinophils, and CRP 1.0 mg/dl. The dose of prednisolone was further reduced to 10 mg and then 5 mg daily. There was no symptom or sign of a recurrent attack as of November 22, when the white cell count was 13,900/mm³ with 6.0% eosinophils, and prednisolone was discontinued.

Discussion

Here we describe four Japanese cases whose clinical features are very similar to those previously reported as episodic angioedema with eosinophilia (2, 5, 6). The characteristic features in the present cases include 1) young women between the ages of 25 and 33, 2) episodic occurrence of edema with body weight gain, 3) leukocytosis with marked eosinophilia, 4) no immunological abnormalities, including IgE, IgM, and CH₅₀, 5) no involvement of vital organs, including heart, lungs, kidneys, and liver, 6) benign course with spontaneous remission or low-dose prednisolone treatment. The underlying disorders causing edema, such as heart, kidney, and liver diseases, and the causes for eosinophilia, such as allergy, parasite, and collagen diseases, were ruled out.

There are several differences in the clinical findings between the present patients and those reported previously (2, 5, 6). First, our patients have had no recurrent attacks, whereas the reported cases had. Secondly, the elevation in serum IgM was not observed in our cases. Thirdly, our patients were not associated with high fever, and only Case 2 had a slight fever. Fourth, the edema in the present patients was not so severe as to cause prominent weight gain. The degree of eosinophilia and leukocytosis was also less than that observed in the previously reported cases. However, the clinical features were otherwise identical to those reported by others (2, 5, 6), and we believe that they belong to the same syndrome. There have also been several other Japanese cases reported in Japanese journals. The clinical features of these Japanese patients are essentially the same as those reported by Gleich et al., and we could not find any characteristics that are unique to Japanese patients with episodic angioedema with eosinophilia. The syndrome we have described is clearly distinct from the so-called hypereosinophilic syndrome, which is characterized by persistent eosinophilia of greater than 1,500/mm³ for
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longer than 6 months and presumptive signs and symptoms of parenchymal organ involvement, such as heart and lungs, and poor prognosis (3, 4).

Although the exact pathogenesis is unclear, it is hypothesized that a product(s) of activated T-cells acts on eosinophils and that degranulation of eosinophils and the subsequent release of eosinophil major basic protein lead to connective tissue damage, cutaneous lesions, increase in vascular permeability, and edema. It is also tempting to speculate the involvement of interleukin-2 (IL-2), based on the observation that the systemic administration of IL-2 causes abnormalities such as fever, edema and weight gain, eosinophilia, and erythematous rash with pruritus, which were all observed in the syndrome of episodic angioedema with eosinophilia (7).

In conclusion, we propose that the syndrome of episodic angioedema with eosinophilia is not rare and that this new clinical entity should be widely recognized for accurate and prompt diagnosis.

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References