A Case of Nonepisodic Angioedema With Eosinophilia Associated With Livedo Reticularis and Erythema Before Onset of Edema of the Legs

Hideki Maejima, MD; Kensei Katsuoka, PhD

Practice Points

- In our analysis, approximately 10% of patients with angioedema with eosinophilia presented with cutaneous eruptions on the legs prior to the onset of edema.
- Angioedema with eosinophilia can be diagnosed at an early stage in young patients who present with eosinophilia and pruritic eruptions of unknown causes on the legs.

The cause of angioedema with eosinophilia (AE) is unknown. Patients with AE sometimes develop pruritic eruptions or urticaria before the onset of edema. We report a case of a 37-year-old woman with nonepisodic AE who presented with erythema and livedo reticularis before the onset of edema. The patient noticed erythema on both heels as well as livedo reticularis on her right great toe 1 month prior to presentation. A biopsy specimen from the heel revealed numerous eosinophils with degranulation infiltrating the subcutaneous tissue. One month later, she developed edema on the legs. Histopathologic findings of biopsy specimens obtained from the legs revealed edema and eosinophils in the subcutaneous tissue.

Some patients with AE present with pruritic eruptions prior to the onset of edema. The diagnosis of AE in our patient with leg edema of unknown cause was considered prior to the appearance of any pruritic eruptions.

Cutis. 2014;93:33-37.

From the Department of Dermatology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan.
The authors report no conflict of interest.
Correspondence: Hideki Maejima, MD, Department of Dermatology, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa, 229-0327 Japan (hm4765@yahoo.co.jp).

Episodic angioedema with eosinophilia (AE) was first described by Gleich et al[1] and is characterized by recurrent angioedema, urticaria, fever, and weight gain. During AE episodes, eosinophilia causes a remarkable increase in leukocyte counts, and the accumulation of edema fluid can lead to weight gain. The clinical course is benign with no involvement of the internal organs. Pruritic eruptions are well known to appear before the onset of edema in some AE patients. We report a case of a 37-year-old woman with AE who presented with erythema on both heels and livedo reticularis on the right great toe prior to the onset of edema on both legs.

Case Report

A 37-year-old woman presented with pruritic erythema on the heels (Figure 1) and livedo reticularis on the right great toe of 1 month's duration (Figure 2). Her medical history was remarkable for allergic rhinitis that had been diagnosed 2 years prior. A biopsy specimen from the heels revealed numerous plasma cells and eosinophils with degranulation in the subcutaneous tissue (Figure 3). Toluidine blue staining revealed metachromatic and degranulated mast cells, and staining studies for anti–major basic protein (MBP) and anti–eosinophil cationic protein (ECP) were positive (Figure 4). Laboratory test results revealed an elevated white blood cell count of 10,900/mm^3 (reference range, 4000–9000/mm^3)

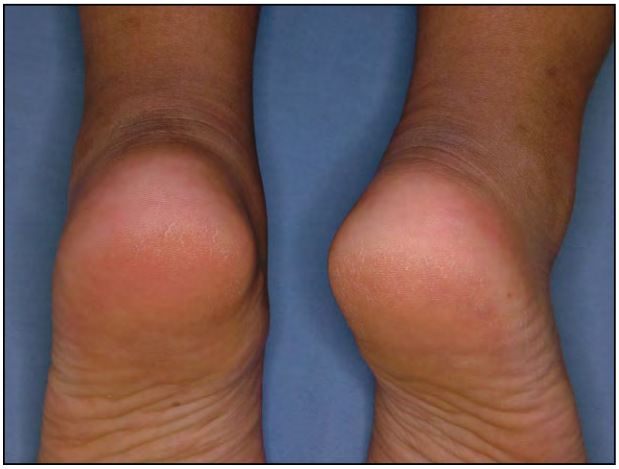

Figure 1. Redness and multiple erythematosus lesions fused and formed an irregular erythematous eruption on the heels.

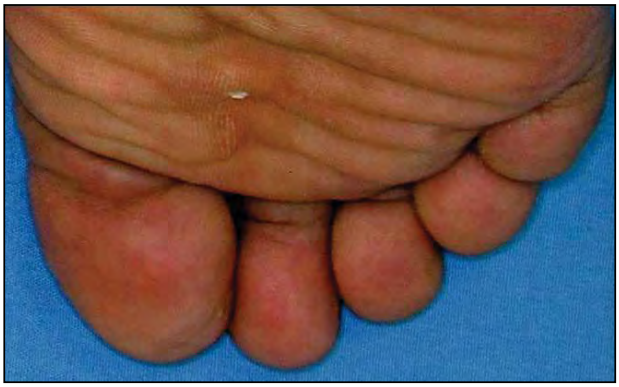

Figure 2. Livedo reticularis with tenderness was present on the right great toe.

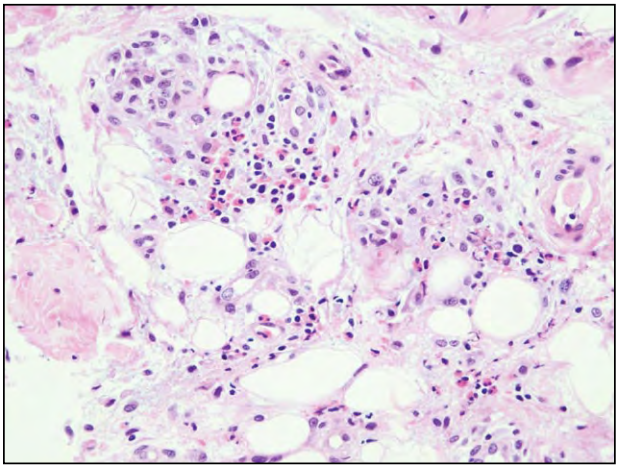

Figure 3. Numerous eosinophils, mast cells, and lymphocytes noted around the blood vessels (H&E, original magnification ×200).

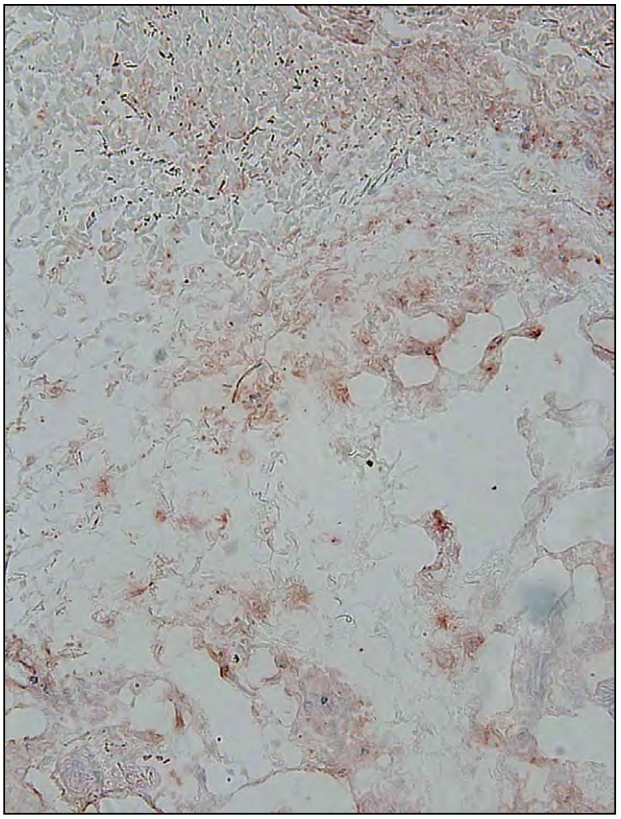

Figure 4. Some cells were positive for anti–eosinophil cationic protein antibody on immunohistochemical staining (immunoperoxidase, original magnification ×200).

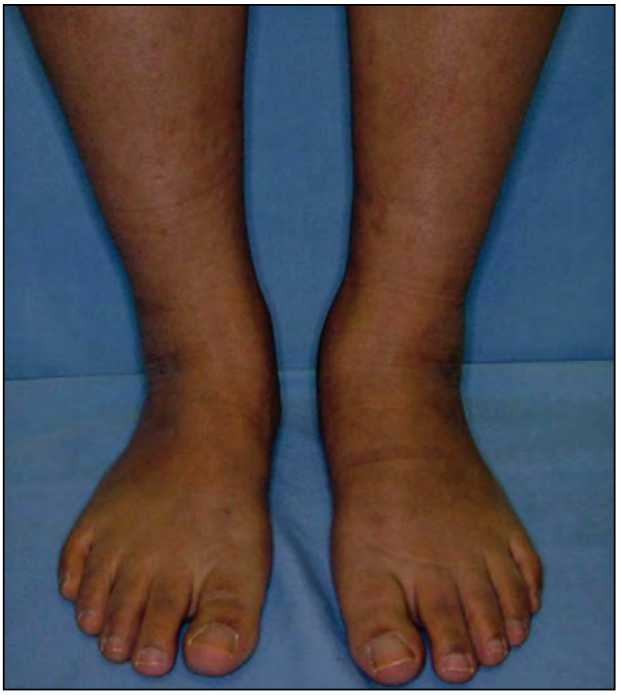

Figure 5. Edema appeared on both legs before administration of oral prednisolone.

Table 1.

Patient's Laboratory Test Results

Laboratory Test	Reference Range	At Presentation	Day 12[a]	Day 19[b]	Day 31	Day 38	Day 58
WBC (/mm^3)	4000–9000	10,900	16,500	17,800	8700	9900	7000
Eosinophils (/mm^3)	0–700	4338	9768	8562	638	743	567
Eosinophils (%)	2.0–6.0	39.8	59.2	48.1	7.5	7.5	8.1
ECP (μg/L)	5.5–14.7 μg/L	ND	ND	150	62.2	ND	47.1
LDH (U/L)	177–229	212	ND	311	152	ND	ND

Abbreviations: WBC, white blood cell count; ECP, eosinophil cationic protein; ND, not detected; LDH, lactate dehydrogenase.
[a]Edema in both legs at day 12.
[b]Oral prednisolone was administered at day 19.

with an eosinophil count of 4338/mm^3 (reference range, 0–700) (39.8% [reference range, 2.0%–6.0%]) (Table 1). Approximately 2 weeks later, asymptomatic swelling appeared on both legs (Figure 5). Skin biopsy specimens showed edema in the upper dermis and a few infiltrating neutrophils and some degranulated eosinophils in the subcutaneous tissue; however, no infiltrating cells were observed in the fascia. Laboratory test results at day 19 revealed an elevated white blood cell count of 17,800/mm^3, with an eosinophil count of 8562/mm^3 (48.1%) and an elevated serum ECP level of 150 μg/L (reference range, 5.5–14.7 μg/L). Liver function tests and urinalysis, as well as serum IgG, IgA, IgM, and complement levels, were within reference range. Chest radiography, electrocardiography, and echocardiography findings were unremarkable. Notably, the patient had gained 3 kg in 1 month. Because oral antihistamines were ineffective and the patient had no other systemic diseases, she was treated with oral prednisolone 15 mg daily. At day 31, the pruritic eruptions began to resolve.

Comment

A variant of AE, nonepisodic AE was first described by Chikama et al.[2] The differential diagnosis includes hypereosinophilic syndrome, eosinophilic cellulitis, and hereditary angioedema. Hypereosinophilic syndrome is characterized by eosinophilia (eosinophil count >1500/mm^3) with no apparent cause, lasting for more than 6 months. This disease is related to endomyocardial fibrosis, eosinophilic vasculitis, thrombosis, and embolic phenomena, and skin lesions are varied. Our case was not consistent with this diagnosis, as the eosinophilia had been present for more than 2 weeks and there was no vascular disease. Eosinophilic cellulitis is characterized by dense eosinophilic dermal infiltrates and eosinophilic flame figures. Our case did not show these findings on histopathology. In hereditary angioedema, low complement levels are seen, but in our case, they were within reference range.

We analyzed the characteristics of cutaneous eruptions that appeared prior to the onset of edema in 150 AE patients: 139 Japanese patients who had been previously reported in Japan[2-7] and 11 patients who had been treated in our clinic (Table 2). Of 150 patients, 23% (35/150) had episodic AE, while the other 115 patients had nonepisodic AE. Additionally, 15.3% (23/150) of patients had cutaneous eruptions prior to the onset of edema. The interval between the onset of the eruptions and the onset of edema generally was within 1 month, ranging from 4 days to 1 year (mean interval, 40 days). Fifteen (10%) patients had an eruption (other than urticaria) before the onset of edema. The mean interval from the onset of erythema to the onset of edema was 18 days. To our knowledge, there are no reports of livedo reticularis occurring prior to the onset of edema in AE patients.

Table 2.

Cutaneous Eruptions Prior to the Onset of Edema in Patients With Angioedema With Eosinophilia (N=150)

	Total No. of Patients (M:F Ratio)	No. of Patients With Urticaria	No. of Patients With Urticarial Erythema	No. of Patients With Erythema With Pruritus	No. of Patients With Papules	Total No. of Cutaneous Eruptions (%)
Our clinic[a]						
NEAE	10 (1:9)	0	0	1	2	3 (30)
EAE	1 (0:1)	0	0	0	0	0 (0)
Total	11 (1:10)	0	0	1	2	3 (27.3)
Report of cases in Japan[2-7]						
NEAE	105 (1:104)	7	6	3	0	16 (15.2)
EAE	34 (10:24)	1	1	2	0	4 (11.8)
Total	139 (11:128)	8	7	5	0	20 (14.4)
Total						
NEAE	115 (2:113)	7	6	4	2	19 (16.5)
EAE	35 (10:25)	1	1	2	0	4 (11.4)
Total	150 (12:138)	8	7	6	2	23 (15.3)

Abbreviations: M, male; F, female; NEAE, nonepisodic angioedema with eosinophil; EAE, episodic angioedema with eosinophilia.
[a]Reported at the Department of Dermatology, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan.

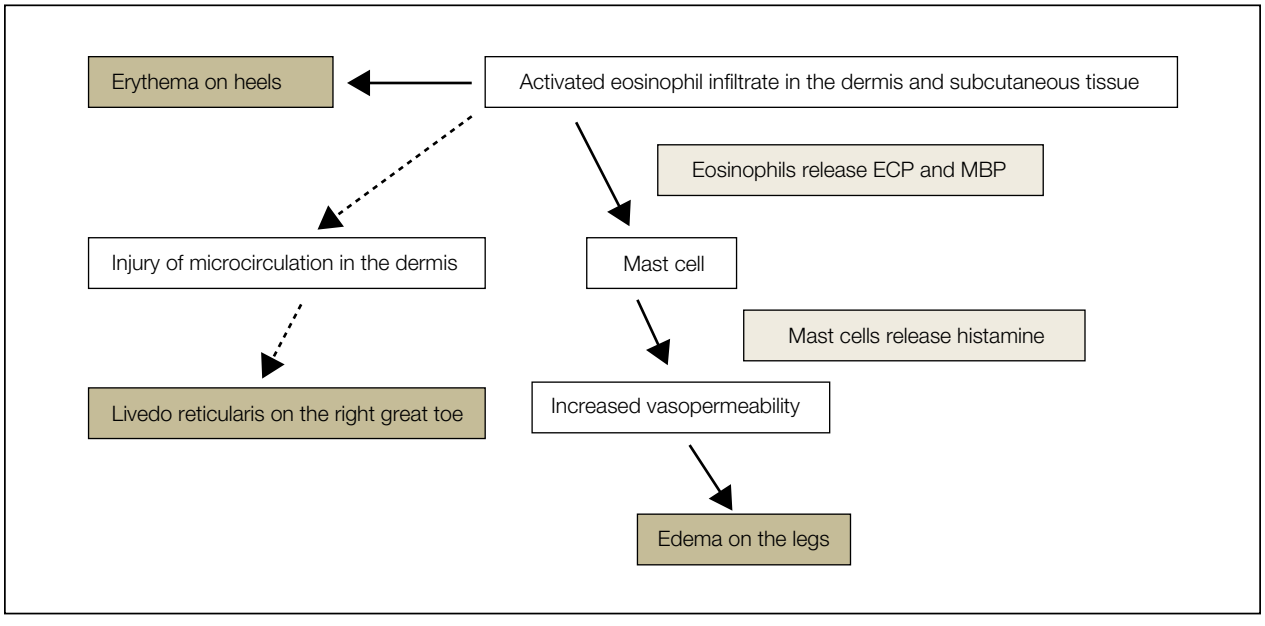

Figure 6. The pathogenesis of our patient. ECP indicates eosinophil cationic protein; MBP, major basic protein.

Elevated serum levels of IL-5, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α, ECP, and MBP previously have been reported in patients with AE.[6-8] IL-5 and granulocyte-macrophage colony-stimulating factor regulate the production and function of eosinophils,[9,10] but the etiology of AE remains unclear. The serum ECP level in our patient was elevated after the AE episode. After the oral prednisolone was administered, the leg edema disappeared and serum ECP levels decreased but still were not within reference range at day 31. The specific granules of human eosinophils contain MBP and ECP, which are released from a persistently high number of eosinophils in the peripheral blood by degranulation. Eosinophil cationic protein acts on mast cells and causes histamine release.[11] Eotaxin stimulates eosinophils, which releases MBP.[12] Human MBP can induce histamine release in vitro from human basophils and rat mast cells.[13] Angioedematous and urticarial lesions are thought to be induced by mast cell degranulation and the release of inflammatory mediators (Figure 6).[14] In our analysis, 10% of AE patients presented with cutaneous eruptions on the legs prior to the onset of edema (Table 2). Based on these findings, AE can be diagnosed at an early stage in young patients with eosinophilia and pruritic eruptions of unknown causes on the legs.

REFERENCES

1. Gleich GJ, Schroeter AL, Marcoux JP, et al. Episodic angioedema associated with eosinophilia. *N Engl J Med*. 1984;310:1621-1626.
2. Chikama R, Hosokawa M, Miyazawa T, et al. Nonepisodic angioedema associated with eosinophilia: report of 4 cases and review of 33 young female patients reported in Japan. *Dermatology*. 1998;197:321-325.
3. Igawa T, Hashimoto Y, Yamamoto A, et al. A case of non-episodic angioedema with eosinophilia [in Japanese]. *Jpn J Clin Dermatol*. 2007;61:876-879.
4. Nakai K, Yoneda K, Moriues T, et al. Nonepisodic angioedema associated with eosinophilia [in Japanese]. *Practical Dermatol*. 2009;31:57-60.
5. Kimura Y, Saito K, Konohana I, et al. A case of episodic angioedema associated with eosinophilia [in Japanese]. *Jpn J Clin Dermatol*. 1999;53:117-119.
6. Mizukawa Y, Shiohara T. The cytokine profile in a transient variant of angioedema with eosinophilia. *Br J Dermatol*. 2001;144:169-174.
7. Okubo Y, Sato E, Hossain M, et al. Periodic angioedema with eosinophilia: increased serum level of Interleukin 5. *Intern Med*. 1995;34:108-111.
8. Butterfield JH, Leiferman KM, Abrams J, et al. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. *Blood*. 1992;79:688-692.
9. Walsh GM. Mechanisms of human eosinophil survival and apoptosis. *Clin Exp Allergy*. 1997;27:482-487.
10. Weller PF. The immunobiology of eosinophils. *N Engl J Med*. 1991;324:1110-1118.
11. Bhandari CM, Baldwa VS. Relative value of peripheral blood, secretion and tissue eosinophilia in the diagnosis of different patterns of allergic rhinitis. *Ann Allergy*. 1976;37:280-284.
12. Melo RC, Spencer LA, Perez SA, et al. Vesicle-mediated secretion of human eosinophil granule-derived major basic protein. *Lab Invest*. 2009;89:769-781.
13. Motojima S, Tateishi K, Koseki T, et al. Serum levels of eosinophil cationic protein and IL-5 in patients with asthma without systemic corticosteroids. *Int Arch Allergy Immunol*. 1997;114(suppl 1):S55-S59.
14. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood*. 1994;83:2759-2579.