Episodic angioedema associated with eosinophilia*

Fang Liu[1]
Haibo Liu[1]
Hong Sang[1]
Wenxing Hu[1]
Min Zhang[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20174351

Abstract: We report a 12-year-old girl who presented with recurrent angioedema on the face, trunk, and extremities, and concomitant marked weight gain for 5 years. During the episode, her white blood cell count increased to 47.7×109/L with 89.9% eosinophils, followed by elevated serum level of IL-5, IgE, IgM, and LDH. Histopathology showed perivascular eosinophilic infiltration and diffuse eosinophilic infiltration throughout the dermis. Possible causes of hypereosinophilia and eosinophilic infiltration of vital organs were ruled out. We also tested the FIP1L1/PDGFRα and ETV6/PDGFRβ fusion gene to exclude the possibility of myeloid and lymphatic vessel neoplasms. The patient was treated with methylprednisolone and discharged with an oral prednisolone taper, which resulted in complete remission of the edema and normalization of peripheral blood eosinophil count, serum IL-5 level, IgE, IgM, and LDH.
Keywords: Interleukin-5; Eosinophilia; Angioedema

INTRODUCTION

Episodic angioedema with eosinophilia (EAE), also known as Gleich syndrome, is a rare and benign disease without involvement of the internal organs. Because of the absence of systemic involvement, clinicians can differentiate this syndrome from hypereosinophilic syndrome (HES).[1]

CASE REPORT

A 12-year-old girl was admitted to Jinling hospital in July 2012 due to a recurrent angioedema on the face, trunk, and extremities, with concomitant marked weight gain. Initially, in 2006 she presented with a pruritic erythema over her extremities. Gradually, she developed pronounced nonpitting edema on the face and extremities, often accompanied by arthralgia, beginning in 2010. All symptoms disappeared spontaneously within a few days. The attacks became more severe and frequent, occurring monthly for nearly half a year. She had frequently been diagnosed with urticaria or angioedema and was prescribed oral or systemic glucocorticosteroids. The patient had no personal or family history of atopy and denied drug intake before the onset of her symptoms.

Physical examination revealed bilateral eyelid edematous erythema, angioedema of the face, trunk and extremities, and some pigment on the chin and cheek. The skin of the bilateral lower extremities was dry and rough, with some multiple pigmented macules (Figure 1). Other skin sites were normal.

Laboratory investigation showed an elevated white cell count of 47.7×10^9 ($3.9\text{-}10\times10^9$) cells/L with marked eosinophilia of 42.9×10^9 ($<7.0\times10^9$) cells/L. Serum IgE and IgM were 719.0 (0-150.0) Ig/ml and 9.51(0.4-3.0) IU/ml, respectively. ESR was 34 (0-20.0) mm/h. Rheumatoid factor (RF) was 70.9 (<20.0) IU/ml. The level of LDH was 528 (60.0-240.0) U/L. All plasma autoantibodies examined were negative. Skin prick tests with a battery of standardized allergen extracts were normal. No parasitic diseases were identified (anisakiasis, hookworm, ascariasis, strongyloidiasis, toxocariasis, or

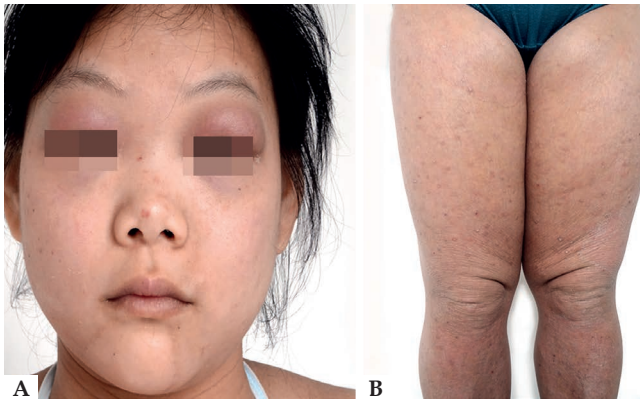

Figure 1: A - Bilateral eyelid edematous erythema; **B -** Angioedema of the extremities with hyperpigmentation

Received on 09.01.2015
Approved by the Advisory Board and accepted for publication on 09.04.2015
* Work performed at the Department of Dermatology, Jinling Hospital affiliated to Nanjing University School of Medicine – Jiangsu, China.
Financial support: none.
Conflict of interest: none.

[1] Department of Dermatology, Jinling Hospital affiliated to Nanjing University School of Medicine – Jiangsu, China.

fascioliasis). The FIP1L1/PDGFRα and ETV6/PDGFRβ fusion gene was negative. Serum C1q esterase inhibitor (C1-INH) activity and C1-INH protein were normal.

Skin biopsy performed in an edematous area of the right lateral thigh revealed perivascular lymphocytic and eosinophilic infiltration and diffused eosinophilic infiltration throughout the dermis with deposition of an eosinophil granule-derived protein and major basic protein (MBP) in immunohistochemistry (Figure 2). Bone marrow examination results were normal. Serum IL-5 level was 603 pg/ml (normal range, 0-8 pg/ml) during the outbreak of the disease but returned to 0 pg/ml after the episode.

We ruled out the possibility of eosinophilic infiltration of vital organs and diagnosed EAE based on clinical presentation, laboratory investigations, characteristic histopathological findings, and exclusion of other causes of hypereosinophilia. The patient was given systemic methylprednisolone (40 mg/d) with complete remission of the edema after two weeks. Peripheral blood eosinophil count, serum IL-5, IgE, IgM, and LDH level returned to normal after two weeks of treatment. We discharged the patient with oral prednisolone at 30 mg/day. Prednisolone was tapered, and her maintenance dose is 10 mg once a day. During a 2-year follow-up, she did not develop any internal organ involvement, and her symptoms were controlled without recurrence.

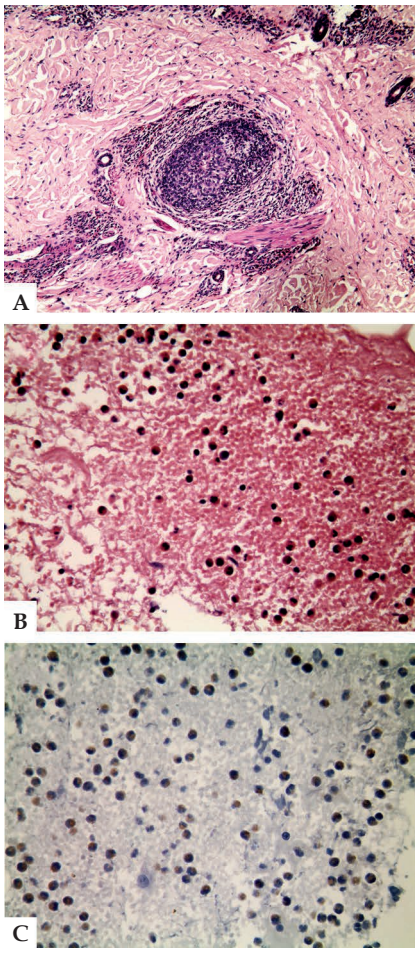

Figure 2: Histopathology showing perivascular lymphocytic and eosinophilic infiltration and diffuse eosinophilic infiltration throughout the dermis, positive for MBP. (**A -** Hematoxylin & eosin X40; **B -** Hematoxylin & eosin X400; **C -** MBP X400)

DISCUSSION

EAE was first described by Gleich in 1984.[2] The majority of cases were reported in the United States, Europe, and Japan.[3]

Our patient was diagnosed with EAE based on the following reasons: the characteristic clinical features including recurrent episodes of angioedema, urticaria and increased body weight; laboratory findings of remarkable elevation of eosinophils, IgM and IgE; and exclusion of underlying disorders causing edema (such as heart, kidney, and liver diseases) and/or hypereosinophilia (such as allergy, parasites, collagen diseases, or hematologic diseases). The absence of ETV6/PDGFRβ and FIP1L1/PDGFRα excluded the possibility of myeloid and lymphatic vessel neoplasms associated with eosinophilia. Our case showed some additional characteristics that were not previously reported in the literature, including accompanying arthralgia, absence of fever, increased serum LDH levels, and positive RF.

EAE should be diagnosed from non-episodic type angioedema with eosinophilia (NEAE), which was proposed by Chikama.[4] NEAE, which is a second type of EAE, has some different characteristics from EAE, including the absence of recurrent attacks, predominance of young females, angioedema localized on the extremities, normal IgM levels, and no necessity for corticosteroid therapy. In 8 out of 11 cases of NEAE described by Nakachi,[5] patients did not receive corticosteroid treatment. He found these patients' eosinophil count returned to normal levels within 8 weeks with no recurrence.

The pathogenesis of EAE is not completely understood. In our patient, IL-5 serum level rose concomitantly with the peak of eosinophilia in the acute phase of the attack. After corticosteroids were started, IL-5 serum level dropped to normal limit, concomitant with the clinical remission and eosinophils. IL-5 is a specific hematopoietic growth factor that is responsible for the growth and differentiation of eosinophils. Several studies have demonstrated that it may participate in the inflammatory reaction of EAE.[1,6] Some studies showed that C5aR, IL-1, IL-6, and soluble interleukin-2 receptor (sIL-2R) also play a role in the pathophysiology of EAE.[1,7]

Corticosteroids remain the first-line therapeutic option for patients with EAE due to their dual suppressive action on eosinophils proliferation and T-cell cytokine production. There is usually a dramatic fall in eosinophil counts and an improvement in EAE symptoms following corticosteroid therapy. Scranton reported 1 case of EAE successfully treated with imatinib mesylate, which was successful for FIP1L1/PDGFRα-positive hypereosinophilic patients.[8] Scranton thought that the good response to imatinib might be due to an imatinib-sensitive mutant kinase similar to that seen in hypereosinophilic syndromes (HES) or chronic myeloid leukemia. He proposed that imatinib could be considered for patients with EAE who require prolonged or recurrent treatment with systemic corticosteroids, even without a demonstrable fusion gene. Our patient was treated with prednisolone and tapered to 10 mg/daily without recurrence and did not develop any internal organ involvement.

Although the rarity of EAE makes it difficult to diagnose, physicians should consider the disease in the case of patients with eosinophilia associated with angioedema. ❑

REFERENCES

1. Banerji A, Weller PF, Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's Syndrome). Immunol Allergy Clin North Am. 2006;26:769-81.
2. Tillie-Leblond I, Gosset P, Janin A, Salez F, Prin L, Tonnel AB. Episodic angioedema associated with eosinophilia. N Engl J Med. 1984 Jun 21;310:1621-6.
3. Abouzahir A, Chaurin P, Coutant G, Garcin JM. Gleich syndrome. A case report and review of the literature. Rev Med Interne. 2005;26:137-40.
4. Chikama R, Hosokawa M, Miyazawa T, Miura R, Suzuki T, Tagami H. Nonepisodic angioedema associated with eosinophilia: report of 4 cases and review of 33 young female patients reported in Japan. Dermatology. 1998;197:321-5.
5. Nakachi S, Inokuma S. Eleven cases of angioedema with eosinophilia treated in a single hospital in Japan. Allergol Int. 2012;61:259-63.
6. Shikiji T, Urano Y, Takiwaki H, Arase S. A case of episodic angioedema associated with eosinophilia. J Med Invest. 1997;44:103-8.
7. Scranton SE, Wild CA, England RW. Episodic angioedema with eosinophilia: successful treatment with imatinib. Ann Allergy Asthma Immunol. 2008;100:172-4.
8. Tillie-Leblond I, Gosset P, Janin A, Salez F, Prin L, Tonnel AB.. Increased interleukin-6 production during the acute phase of the syndrome of episodic angioedema and hypereosinophilia. Clin Exp Allergy. 1998;28:491-6.

Mailing address:
Hong Sang
Department of Dermatology, Jinling
Hospital affiliated to Nanjing University School of Medicine
Nanjing,
210002 Jiangsu, China.
E-mail: sanghong@nju.edu.cn

How to cite this article: How to cite this article: Liu H, Hu W, Liu H, Zhang M, Sang H. Episodic angioedema associated with eosinophilia. An Bras Dermtatol. 2017;92(4):534-6.