Non-episodic angioedema associated with eosinophilia

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DESCRIPTION
A Japanese woman in her 30s presented with a 1-week history of progressive peripheral oedema of the hands and feet in October. She reported difficulty in clenching her fists and was unable to wear her wristwatch or shoes because of oedema. She also experienced paroxysmal urticaria in the distal extremities, including the palms and soles, and mild weight gain. She denied fever, facial oedema, exertional dyspnoea and arthralgia. She had no personal or family history of hereditary angioedema or any allergic diseases and was receiving no medications. Physical examination revealed symmetrical, non-pitting oedema in both hands and lower legs (figure 1A). There was no facial swelling. An examination denied any skin rash. The rest of the physical examination was unremarkable. Laboratory findings revealed an elevated white blood cell count (13.9 × 10⁹/L) with 47% eosinophils (absolute eosinophil count, 6533/μL) and an elevated lactate dehydrogenase value of 257 (reference range: 124–222) IU/L. Serum IgM and IgE, liver enzymes, urinalysis, serum complement and serum vitamin B12 level were normal. An ECG, X-ray of the chest and serum cardiac troponin were normal. Nephrotic syndrome, thyroid disease and parvovirus B19 infection were ruled out. Based on these findings, non-episodic angioedema associated with eosinophilia (NEAE) was clinically diagnosed. Her symptoms spontaneously improved without treatment, and her oedema almost completely resolved 2 weeks after her first visit (figure 1B). Her eosinophil level normalised after another 6 weeks.

NEAE, a subtype of angioedema associated with eosinophilia, as well as episodic angioedema with eosinophilia (EAE),1 is an important differential diagnosis in patients with acute-onset peripheral oedema. The prevalence of NEAE remains unknown although at least 100 cases have been reported mostly in women from Japan, Korea and Thailand.2 Although the precise pathophysiology remains unknown, NEAE is thought to stem from an aberrant immune response to some exogenous stimulus, such as an infection, environmental factor, genetic susceptibility or the influence of sex hormones.2 Several cytokines and chemokines, including interleukin 5, thymus-regulated and activation-regulated chemokine/C-C motif chemokine ligand-17, tumour necrosis factor-a and vascular endothelial growth factor (VEGF), are involved in generating the symptoms.3

NEAE can usually be diagnosed clinically despite the absence of established diagnostic criteria because its clinical features are quite characteristic.

Figure 1 Symmetrical, non-pitting oedema of the hands (A) was observed at the initial presentation. Peripheral oedema resolved completely 2 weeks after the first visit (B).

The oedema is usually non-pitting and occurs only from the wrists and knees down, and the eosinophilia is usually severe despite the patient’s good general health.

NEAE resembles EAE in some respects, including having a predominantly peripheral distribution, eosinophilia and a benign prognosis without internal organ involvement.1 4  However, there is a crucial difference between the two conditions; while EAE frequently recurs and usually requires steroid therapy, patients with NEAE usually experience only a single episode, which frequently remits spontaneously within a few weeks to months without specific therapy despite the severe type possibly requiring low-dose steroid or antihistamine therapy.1 5 Therefore, distinguishing the two conditions is of value. Several characteristics are helpful in distinguishing NEAE from EAE: first,
NEAE occurs predominantly in young women of East Asian descent; second, NEAE has no facial involvement and almost always shows a normal serum IgM level; and third, about half of patients with NEAE experience transient arthralgia, whereas no patients with EAE do. Moreover, around 70% of reported cases of NEAE, including the present case, occurred in the autumn, a potentially useful diagnostic clue whose pathological significance, if any, remains unknown.

Learning points

► A young, Asian woman with acute-onset peripheral oedema, marked eosinophilia without internal organ involvement and normal serum IgM levels should have a high index of suspicion for non-episodic angioedema associated with eosinophilia (NEAE).
► When NEAE is suspected, patients should be closely observed without treatment to avoid using potentially harmful steroid therapy.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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