Episodic Angioedema with Eosinophilia: Precursor lesions and Relevance of Histology

A Case Report

ULRICH KÜHNE and WOLFGANG CHRISTIAN MARSCH

Zentrum der Dermatologie und Venerologie, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

A 59-year-old patient suffered from persistent angioedema-like swellings and blood eosinophilia. The disease was preceded by an erythema multiforme-like exanthema and urticarial papules. Persistent eosinophilia with exclusion of its known causes and skin biopsy helped to establish the diagnosis of the benign variant of hypereosinophilic syndrome known as 'episodic angioedema with eosinophilia'. Corticosteroid therapy was successful. The therapeutic alternatives are discussed. ***Key words: Major basic protein; Corticosteroids; Hypereosinophilic syndrome.***

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U. Kühne, Zentrum der Dermatologie und Venerologie, Abt. I, Johann Wolfgang Goethe-Universität, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, Germany.

The term 'hypereosinophilic syndrome' (HES) was coined in 1968 by Hardy & Anderson (1). It comprises a spectrum of diseases that are associated with blood eosinophilia. Chusid et al. (2) established the following diagnostic criteria:

1. persistent eosinophilia of $> 1500/mm^3$ for more than 6 months
2. lack of evidence of parasitic, allergic or other known causes of eosinophilia
3. signs and symptoms of organ involvement.

Within this group of diseases a variant with a benign course can be distinguished. It is characterized by a lack of internal organ involvement and a favourable prognosis and has been named 'episodic angioedema with eosinophilia' (3).

In this case report we wish to draw attention to the precursor lesions of this disease and the diagnostic relevance of skin biopsy.

CASE-REPORT

History

A 59-year-old male white hispanic patient who underwent appendectomy in 1947, had hepatitis, in 1951, gastritis in 1967 and herniotomy in 1985.

History of present illness

10/1985. Erythema-multiforme-like exanthema after taking penicillin; 16,000 WBC; 8% eosinophils
1/1986. Urticarial papules in cubital region and on the abdomen; 11,700 WBC; 7% eosinophils
2/1986. Swelling of periorbital region and of the glabella. Diagnosis: angioedema
9/1987. Conjunctivitis and urticaria; 24,900 WBC; 6% eosinophils; IgE 5 kU/l; remission after 100 mg prednisolone i.v.; 2 weeks later, swelling of left hand; 15,800 WBC; 6% eosinophils
10/1987. Swelling of both forearms and face; fever, 38.0°C; 11,700 WBC; 29% eosinophils; IgE 5 kU/l. Intestinal candidiasis treated with nystatin per os; antihistamines without effect on swellings
11/1987. Swellings of forearms, left hand and periorbital regions; 20,600 WBC; 32% eosinophils

Laboratory investigations

Repeated analyses of clinical routine tests incl. serum-electrophoresis, IgG, IgA, IgM, IgE, C3, C1-esterase inhibitor and urinalysis were all within normal range; trichinella antibodies were negative and no parasitic ova or candida could be detected in repeated stool samples.

Other investigations

No abnormalities were found in chest X-ray, ECG, ultrasound cardiogram, sonography of the abdomen, barium examination of upper gastro-intestinal tract, or double-contrast-barium-air enema. Iliac crest biopsy showed no signs of malignancy, but intense eosinophilia. Neurologic examination revealed no abnormalities.

Skin biopsy (11/87, left arm)

Sleeve-like dense perivascular infiltrate by lymphocytes and eosinophilic granulocytes. Characteristic passage of eosinophils through the walls of dilated postcapillary venules. Diffusely distributed eosinophils within the intervascular connective tissue of the corium. Diffuse edema and evenly distributed eosinophils and plasma cells within the lobules of subcutaneous fatty tissue.

Course

As earlier treatment with antihistamines had proved to be ineffective, treatment with 60 mg methylprednisolone with gradual tapering was begun in 11/87. This led to healing of the skin lesions and reduction of eosinophils to 11%, with 9,200 WBC. Relapse occurred immediately after discontinuing the steroids. Under alternating treatment with 8 mg methylprednisolone, there were no skin signs, but an increase of eosinophils (48%, 19,700 WBC in January 1988). In May 1988, 19,000 WBC with 58% eosinophils, after 2 weeks of 20 mg methylprednisolone decreasing to 8,900 WBC with 2% eosinophils. After reduction to 8 mg, alternating, 27,700 WBC with 49% eosinophils. The patient did not return for further observation.

DISCUSSION

This case fulfils the diagnostic criteria of HES (2) with persistent blood-eosinophilia $> 1500/mm^3$ and exclusion of known causes of eosinophilia. Because of the lack of organ involvement it can be classified as 'episodic angioedema with eosinophilia' (3), which is regarded as a benign variant within the spectrum of HES.

A probably penicillin-induced erythema-multiforme-like exanthema appeared 23 months before the first occurrence of significant blood-eosinophilia of more than $1500/mm^3$, as defined by Gleich et al. (3). Three months later, there were urticarial papules in the cubital regions and persistent swellings of the glabella and periorbital regions, together with slight blood-eosinophilia, but insufficient to establish a diagnosis of HES. Other authors also report urticarial or papular eruptions preceding HES (3, 4, 5). The persistence and deep involvement of the urticarial eruptions were reflected histologically by the eosinophilic inflammatory infiltrate in the subcutaneous fatty tissue ('eosinophilic panniculitis'). The absence of lymphocapillary vessels in the subcutaneous tissue could be responsible for the persistence of inflammatory processes located there. The high percentage of histologically detected 'flame-figures' representing major basic protein (MBP) (4 out of 9 cases in the literature), the persistence of edematous swellings for several days, the ineffectiveness of antihistamines and the good reponse to corticosteroids are frequent features of HES (5, 6, 7, 8) and can also be found in Wells syndrome. Possibly a higher percentage of MBP could be detected, if repeated biopsies were taken and more sensitive immunohistochemical techniques using monoclonal antibodies were applied.

The swellings and blood-eosinophilia were responsive to corticosteroids in medium dosage, but the increased dosis necessary to suppress eosinophilia during the disease course may indicate a transition to other, more adverse forms of HES. A possible therapeutic alternative could be DADPS and DNCG (5) or the recently introduced antihistaminic substance cetirizine (Zyrtec®, UCB Kassella-Riedel), which is highly effective against the migration of eosinophils.

The number of blood-eosinophils is probably of only limited value as a parameter for follow-up, due to the kinetic data of eosinophils. After 2–6 days of maturation in the bone-marrow, eosinophils have a half-life of 6–12 h in the blood whence they migrate into tissue where they persist for several days (9). This means that less than 1% of eosinophils can be found in the blood.

Uncharacteristic papular and urticarial eruptions and angioedema-like swellings unresponsive to common antihistamines may precede the development of HES. The skin biopsy showing tissue eosinophilia, including the subcutis and possibly with flame figures representing MBP, can give additional hints towards the correct diagnosis.

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