

Erythema Marginatum Preceding an Acute Oedematous Attack of Hereditary Angioneurotic Oedema

Henriette Farkas¹, George Harmat², Andrea Fáy³, Béla Fekete⁴, István Karádi⁴, Beáta Visy¹ and Lilian Varga⁵

¹Allergology & Angioedema Outpatient Clinic and ³Dermatology Outpatient Clinic, Semmelweis University, Kútvölgyi Clinical Centre, Kútvölgyi út 4., H-1125 Budapest, Hungary. ²First Department of Paediatrics, Madarász Children's Hospital, Budapest, Hungary. ⁴Third Department of Internal Medicine, Semmelweis University, Budapest, Hungary. ⁵Complement Laboratory, National Institute of Haematology and Immunology, Budapest, Hungary. E-mail: farkash@kut.sote.hu

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Sir,

Hereditary angioneurotic oedema (HANO) results from the deficiency of C1-esterase inhibitor (C1-INH) – a protein that prevents spontaneous activation of the classical pathway of the complement system (1, 2). These changes are associated with activation of the kinin, fibrinolytic and coagulation systems, where C1-INH has a regulatory function. The consequential accumulation of vasoactive substances (e.g. C2-kinin, bradykinin) enhances vascular permeability and induces the formation of oedema (3, 4).

The disease is inherited as an autosomal-dominant trait that can manifest as one of two phenotypes. Type I is characterized by low plasma C1-INH level. In Type II, its serum concentration is normal or elevated, but C1-INH activity is low. Regardless of type, clinical manifestations are identical and are characterized by attacks of subcutaneous and/or submucosal formation of oedema (5). Subcutaneous oedema involves the extremities, torso, face and the genital region. Laryngeal oedema can lead to suffocation rapidly. This hazard is responsible for the strikingly high, 20% to 30% mortality. The consequences of gastrointestinal oedema can mimic the clinical picture of an acute abdominal catastrophe (2, 6–9).

In addition to the typical subcutaneous oedema described above, a similarly characteristic, map-like pattern – erythema marginatum – can appear in a proportion of cases. Osler was the first to describe this sign in 1888 as the “red and marbled condition of the skin of the breast” (10). References to this abnormality can be found in many review articles (2, 6, 7), as well as in an analysis of the medical history of two families (11). In the literature, erythema marginatum is mentioned as a characteristic feature of rheumatic fever (12). Comprehensive investigation into the clinical significance and characteristic features of erythema marginatum associated with HANO, as well as diagnostic pitfalls and errors, has not yet been performed, so we have conducted a retrospective analysis on the medical records of 69 HANO patients to explore the clinical properties of this skin abnormality accompanying oedematous attacks.

PATIENTS AND RESULTS

Clinical information on 69 patients (31 men and 38 women; aged 4–69 years) was evaluated. The diagnosis of HANO was established by characteristic clinical manifestations and the results of complement studies. Type I HANO was ascertained in 59 cases, whereas 10 patients suffered from Type II disease. Time of onset, duration and localization of erythema marginatum were analysed. Familial occurrence of the skin lesion and potential correlation with the type as well as the severity

of HANO attacks were assessed. Erythema marginatum associated with oedematous attacks was observed in 29 patients (11 men and 18 women). The skin rash always developed before the onset of the attack, persisted for 24 to 48 h, then disappeared simultaneously with resolution of the oedema. Erythema marginatum accompanied both abdominal attacks and the oedematous swelling of the face, trunk and limbs in 18 cases. In 11 patients, the skin rash developed before or during abdominal attacks only (Fig. 1). Coincidence of erythema with laryngeal oedema was observed in a single case.

Erythema marginatum was confined to the torso in 20 patients, whereas 9 patients had skin rash on the extremities as well (Fig. 2). Although it usually occurs as early as in childhood, three patients started to experience erythema marginatum during early adulthood only.

In a patient of the study population, erythema marginatum developed at the age of 6 weeks and resolved spontaneously after 2 days. Erythema recurred on several occasions until 5 years of age, but the skin lesion was never accompanied by oedema. Attacks of subcutaneous (facial and limb) oedema started after 5 years of age and HANO was diagnosed at the age of 10. In three cases, erythema marginatum was thought to result from allergic pathomechanism and therefore corticosteroid therapy was initiated. Although the efficacy of this treatment was insufficient, HANO was diagnosed years later only. Pedigree-analysis revealed familial clustering of erythema marginatum. Erythema marginatum was absent in 6 out of the 19 families analysed. In 5 families, only one individual was afflicted, whereas the characteristic skin rash was observed in all members of the remaining 8 families.



Fig. 1. Erythema marginatum on the chest wall of a patient during an acute abdominal attack of hereditary angioneurotic oedema.

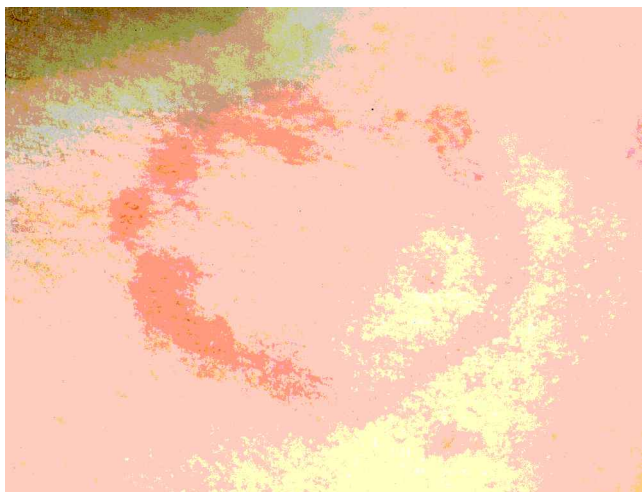


Fig. 2. Close-range photograph of a typical skin lesion.

DISCUSSION

All symptoms and signs conducive to the diagnosis of HANO or that assist the prediction of acute oedematous attacks are helpful clues for the clinician. In a proportion of cases, precipitating factors – such as mechanical trauma, mental stress, the effects of hormones and other drugs (e.g. ACE inhibitors, oral contraceptives) – can be identified in the aetiology of acute attacks (2, 6, 7). Although the latter are usually of sudden onset, a proportion of patients reports prodromal nervousness and mental stress for days preceding the attack. Often, characteristic feeling of distension or pressure occurs in the joints or soft tissue region of subsequent oedema formation. Erythema marginatum – also referred to in the literature as erythema anulare rheumaticum accompanying rheumatic fever – is another helpful symptom that facilitates the early recognition of an impending HANO attack. Typically, a flat, ring-shaped and pale-red lesion is seen; its enlargement can produce a polycyclic, serpiginous – sometimes map-like or reticular – pattern. Occasionally, the border of the erythematous lesion is slightly protuberant – hence it is called erythema marginatum. Its colour suggests a rash that starts fading immediately after eruption. Erythema marginatum is most common on the trunk (13). The lesion has no distinctive histopathologic features (14). As a rule, this eruption can be readily differentiated from other forms of annular erythema (erythema anulare centrifugum, erythema gyratum repens, erythema chronicum migrans) or urticaria (15). The reticular pattern of the rash is similar to that of erythema infectiosum, but the absence of systemic symptoms (low-grade fever, joint pain) and the lack of facial erythema help in distinguishing these two disorders. In our series, erythema marginatum had invariably preceded oedematous attacks and consequently this lesion may be considered a

prodromal sign. Occasionally, however – as demonstrated by a single case in the study population – it can be the initial sign of an acute episode of HANO. Erythema marginatum usually resolves simultaneously with the attack – abdominal oedematous attacks that can mimic an acute abdominal catastrophe and are accompanied by the appearance of free peritoneal fluid, as well as oedema of the intestinal wall. Such attacks often lead to unwarranted emergency surgery and are commonly preceded by the occurrence of this skin rash. Nevertheless, the latter is not predictive of the severity of the impending attack. Familial clustering is possible – it has been demonstrated among the relatives of one patient in this series.

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