

A Female with Hereditary Angioedema Developing Wheals: A Case Report

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According to the recent EAACI/GA²LEN/EDF/WAO urticaria guideline “urticaria is a disease characterized by the development of wheals (hives), angioedema, or both. Urticaria needs to be differentiated from other medical conditions in which wheals, angioedema, or both can occur as a symptom, for example skin prick test, anaphylaxis, auto-inflammatory syndromes, or hereditary angioedema (bradykinin-mediated angioedema)” (1). It has long been clinical dogma that bradykinin-mediated forms of angioedema never present with wheals (2). We discuss here an interesting case that questions these definitions.

CASE REPORT

A 55-year-old woman was referred to us by a haematologist for a second opinion regarding wheals. She had a history of hereditary angioedema type 1 (C4 110 mg/l reference values 150–400, C1 q 117 reference values 81–128, C1 esterase inhibitor 0.29 E/ml reference values 0.76–1.33), diagnosed at age 16 years. Both her daughters and granddaughters have hereditary angioedema. Since 1983 (30 years previously) she had been treated with danazol 3 times a week with good results. Four years before presentation at our patient clinic she was treated successfully for mamma carcinoma with surgery and subsequent radiotherapy and furthermore had an allergy to dust mites. When the menopause started she developed uterus myomatosis and medical treatment was adjusted to 200 mg danazol daily and cyclokapron 500 mg 2 times daily. One and a half years previously she developed pruritic skin lesions, which come and go within 24 h (**Fig. 1**). There was no time relationship between the pruritic skin lesions and angioedema attacks, therefore we consider the pruritic skin lesions not to be a prodromal symptom. She was treated with the subsequent antihistamines: levocetirizine 5 mg 2 times daily, ranitidine 150 mg 2 times daily, fexofenadine 120 mg 1–2 times daily and desloratadine 5 mg once daily, with insufficient results. Because wheals were described as a side-effect of danazol, treatment was stopped half a year before she presented at the outpatient clinic. Cyclokapron was slowly increased; however, the wheals and angioedema increased in frequency. The patient was treated with an injection of plasma-derived human C1 inhibitor concentrate in the event of angioedema. She had had this emergency medication at hand for the last 20 years. Three weeks earlier cyclokapron was stopped. After restarting



Fig. 1. Wheals on the upper leg.

danazol combined with levocetirizine daily, 4 times 5 mg, both angioedema and wheals subsided.

DISCUSSION

The patient was diagnosed as having 2 problems concurrently: first, hereditary angioedema based on a C1 esterase inhibitor deficiency presenting as angioedema, starting during her teenage years; and, secondly, since 1.5 years, urticaria presenting as wheals. Hereditary angioedema and urticaria are considered as 2 different problems based on differences in their pathomechanisms (3, 4). Based on these different pathomechanisms C1 esterase inhibitor deficiency may not be regarded as a subtype of urticaria. However, this case demonstrates that both pathomechanisms can occur simultaneously.

Erythema marginatum, a reticular and serpiginous, usually asymptomatic, erythema is described as a prodromal symptom of hereditary angioedema (5, 6). The wheals

our patient experienced were distinct from erythema marginatum due to their transient, widespread and pruritic nature. In addition, no time relationship was recounted between pruritic skin lesions and angioedema attacks.

Wheals are described as a side-effect of danazol. Nonetheless, in this patient it is unlikely that this medication was causing the wheals, because the medication was used for more than 30 years and wheals persisted for 6 months after discontinuation of danazol. Paradoxically angioedema is also described as a side-effect of danazol.

Time-wise, a relationship between myomas and worsening of hereditary angioedema is suggested. However, it could be that the menopause worsened the angioedema. The PREHAET study reported that menopause improved hereditary angioedema in 13% of patients and worsened it in 32% (evidence level III) (7). There are no studies available on the prevalence of urticaria in perimenopausal, menopausal and postmenopausal women (8). It is most likely that the urticaria should be regarded as a separate event with unknown trigger. In the patient described here the urticaria was difficult to treat using low doses of antihistamine, as is seen in many cases. The increase in the dose of antihistamines may account for the treatment response of urticaria, while reinstatement of danazol treatment accounts for reduction in the symptoms of hereditary angioedema.

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