Acquired C1 inhibitor deficiency (AAE) is a rare syndrome with features similar to those of hereditary angioedema (HAE), but differing in its later onset and lack of family history. AAE is characterized by increased consumption of C1 inhibitor associated with lymphoproliferative or malignant disorders, autoimmune or infectious diseases (1, 2).

In C1 inhibitor deficiency two different skin manifestations can be seen: angioedema and erythema marginatum. Erythema marginatum is a highly characteristic serpiginous, non-pruritic exanthema, also known as chicken wire erythema, reported by up to 60% of patients (3). Erythema marginatum may precede or accompany the angioedema attack or it can be an isolated finding.

Bradykinin is a key mediator in these angioedema attacks (4), and deposits of bradykinin have been identified in a skin biopsy of erythema marginatum (5). Icatibant, a bradykinin-B2-receptor antagonist, is an emerging treatment option in C1 inhibitor deficiency, licensed in Europe in 2008 for the indication HAE.

CASE REPORT

A 61-year-old man was referred to us in 2008 with a history of swellings of his hands, feet and external genitalia every 3–4 months for the last 4 years. The attacks were typically preceded or accompanied by a serpiginous erythema. During the last year his swellings had become more frequent and he had experienced recurrent, disabling angioedema of his face and painful abdominal attacks. Treatment with antihistamines and corticosteroids had no effect and the swellings disappeared after 1–3 days with or without treatment. A suspicion of C1 inhibitor deficiency was raised and blood tests revealed a functional C1 inhibitor value of 48%, but normal C1 inhibitor, C1q and C4c concentrations. At re-test one year later, functional C1 inhibitor value was <20% (70–130), C1 inhibitor concentration was 0.06 g/l (normal values 0.21–0.39), C4c was 0.08 g/l (0.10–0.40) and C1q was <0.01 µg/l (0.29–0.60) and AAE was diagnosed. Auto-antibodies (IgM and IgG) against C1 inhibitor were detected in high titres. Our patient had been treated for a superficial malignant melanoma 2 years previously, but no signs of relapse could be demonstrated. Work-up with blood tests including ANA, chest X-ray, ultrasonography of the abdomen and positron emission tomography – computed tomography (PET-CT) was unremarkable. The patient started prophylactic treatment with tranexamic acid 1000 mg tid in April 2009 with sparse effect and frequency of attacks steadily increased until he needed C1 inhibitor concentrate (Berinert®, CSL Behring, Marburg, Germany) almost weekly for acute attacks. Almost every angioedema attack was preceded or accompanied by erythema marginatum, disappearing 3–4 h after the injection of 1500 units of C1 inhibitor concentrate.

In December 2009, he presented with a scrotal angioedema of 1-day duration and a concomitant erythema marginatum on his neck and trunk. He received subcutaneous treatment with icatibant (Firazyr®, Jerini, Berlin, Germany) 30 mg, and the erythema marginatum surprisingly disappeared within 15–30 min (Fig. 1). The scrotal edema started to decrease after 4 h. Besides a transient slightly painful urticarial injection-site reaction (Fig. 2), no side-effects to the drug have been observed in this patient. Until now he has received a total of 11 individual treatments with icatibant for facial, tongue and abdominal swellings, with a fast treatment response in all situations. In the last four attacks local injection-site reactions and erythema marginatum were not seen. At the time of writing he develops angioedema every 3–4 weeks. No underlying cause of his AAE has yet been identified.

DISCUSSION

The prophylactic and symptomatic management of AAE correspond to treatment of HAE, but the treatment response may be different. AAE patients are often resistant
to attenuated androgens, thus the first choice for angiodema prophylaxis is an antifibrinolytic agent (1, 2).

C1 inhibitor concentrate has been the treatment of choice for angioedema attacks in AAE patients; however, some patients have autoantibodies against C1 inhibitor and become highly resistant, thus doses have to be increased several times in order to obtain a clinical response. The effect of icatibant on angioedema attacks in AAE has been published in three case reports earlier this year; however, in none of these patients was erythema marginatum described (6–8). The drug is not yet licensed in AAE, but its mechanism of action also makes icatibant a treatment choice in AAE.

This is the first report showing treatment response of icatibant on erythema marginatum confirming bradykinin as a key mediator, not only in angioedema attacks of C1-inhibitor deficiency, but also in erythema marginatum.

Conflict of interest: The authors have been involved in clinical research or educational events involving CSL Behring and Jerini/Shire.

REFERENCES