



Clinical Pearls

Chronic spontaneous urticaria and angioedema requiring treatment with omalizumab in a patient with hereditary angioedema



Clinical Presentation

A 27-year-old woman with a history of hereditary angioedema (HAE), diagnosed at the age of 15 years, is routinely followed up in Immunology clinic. She initially presented with a 3-year history of recurrent angioedema of the extremities and episodic acute abdominal pain with nausea and vomiting. Although there was no clear family history of HAE, she noted that her father had experienced swelling of the hand years before but had not sought medical attention for this. Both parents were advised to have C1 esterase inhibitor level and function tested, however, have not yet done so.

Initial investigations revealed a reduced C4 level (0.06 g/L; reference range, 0.14–0.54 g/L) and reduced C1 esterase inhibitor level (0.06 g/L; reference range, 0.15–0.35 g/L) and function (<30%; reference range, 70%–150%). Subsequently, genetic testing of the C1 inhibitor gene (*SERPING1*) demonstrated deletion of exon 2, an uncommon mutation consistent with a diagnosis of type 1 HAE.

Initial management consisted of withdrawal of the combined oral contraceptive (COCP) and she was provided with standby C1 inhibitor concentrate to treat acute episodes of angioedema. At routine follow-up, she reported good overall control of her HAE with no episodes of angioedema following withdrawal of the COCP.

Four years later she described a one-month history of a widespread pruritic erythematous rash and on examination, an urticarial rash was present over the trunk and limbs. The urticaria was associated with angioedema of the lips, hands and feet that was distinct from the angioedema she had previously experienced during attacks of HAE. She was diagnosed with chronic spontaneous urticaria (CSU) with angioedema on a background of a known history of HAE.

Clinical Outcome

The patient began long-acting, nonsedating antihistamine treatment, up to 4 times the usual licensed dose. Her condition followed a relapsing-remitting course for several years before becoming more severe and persistent, at which time the leukotriene antagonist, montelukast, was added to her treatment. She continued to experience urticaria with an angioedema and urticaria activity 7 score (UAS7) of 37 despite this treatment. She completed 6 months of treatment with anti-IgE therapy (omalizumab) with an

excellent clinical response. The UAS7 decreased to 2, and she remains well and free of urticaria 1 month after completion of treatment. She is likely to require further courses of omalizumab if the CSU returns. She continues to hold treatment for HAE and has available icatibant and C1 inhibitor concentrate.

HAE is a rare condition, with a prevalence of approximately 1 in 50 000, characterized by attacks of angioedema *without* urticaria. The attacks often involve swelling of the subcutaneous tissues and mucosa of the gastrointestinal and upper respiratory tract. Laryngeal involvement can be life-threatening.^{1,2} In contrast, urticaria is commonly encountered. CSU is the presence of urticaria for more than 6 weeks with no obvious stimulus.^{3,4} CSU can be further subdivided into patients who present with only urticaria, those who present with urticaria and angioedema, and patients with angioedema alone.³ Patients with angioedema and urticaria and those with angioedema alone often have a worse prognosis with regard to longer duration of symptoms before disease remission.⁵ The angioedema associated with HAE is mediated by bradykinin, whereas angioedema associated with CSU is histamine-mediated.

The patient in the case presented could discriminate between angioedema experienced in the context of CSU from that attributable to HAE. The absence of urticaria is a key feature of HAE, and patients presenting with angioedema without urticaria warrant investigation for C1 inhibitor deficiency.¹ Patients with HAE can develop a rash known as erythema marginatum, although this was not present in this case.⁶

With a UAS7 greater than 28, demonstrating poorly controlled chronic urticaria despite treatment with antihistamines and leukotriene receptor antagonist, the patient began anti-IgE therapy.

Previous cases of chronic urticaria in patients with HAE have been reported, but to our knowledge this is the first reported case of CSU and angioedema treated with anti-IgE therapy in a patient with HAE.^{7,8} The case demonstrates the distinct pathophysiologic processes and management approaches of HAE and angioedema associated with CSU.

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