



Letters

Not every angioedema following urticaria is histamine-mediated

A 27-year-old woman experiencing angioedema attacks without concomitant urticaria since the age of 7 years was diagnosed as having hereditary angioedema (HAE) type II in our clinic in 2014. She did not have any siblings. Her mother was also diagnosed as having type II HAE in our clinic. On admission, she was complaining of frequent recurrent angioedema of her extremities and lips and episodic abdominal pain with nausea and vomiting, which was occasionally concomitant.

Initial investigations revealed a reduced C4 level (0.06 g/L; reference range, 0.1–0.4 g/L), normal C1 esterase inhibitor (C1 INH) level (35.1 mg/dL; reference range, 18–40 mg/dL) and low C1 INH function (15%; reference range, 60%–130%). A point mutation, c.1397 G>A, on exon 8 of the C1 INH gene (*SERPINC1*) was found, confirming the diagnosis of type II HAE. Her acute attacks were treated with C1 INH concentrate on demand, and she was provided tranexamic acid 1000 mg/day for long-term prophylaxis after experiencing severe laryngeal edema in 2016.

After 1 year, the patient received 30 mg icatibant the second time for an abdominal pain attack, after which she experienced an immediate itchy wheal of 20 cm in diameter and a flare at the injection site, which resolved in 24 hours after taking a short-acting antihistamine and methylprednisolone. She was confirmed as having immunoglobulin E-mediated hypersensitivity to icatibant after a positive skin prick test result compared with the negative results in healthy controls, although its predictive value is unknown (Fig 1).

After 2 years, she started experiencing urticarial plaques, and after diagnostic workup, she was also diagnosed as having chronic spontaneous urticaria (CSU). Despite a positive autologous serum skin test result, all laboratory findings and physical urticaria challenge test results were normal. She reported good overall control of urticaria with a daily dose of 5 mg of levocetirizine. However, during follow-up, when she ceased taking antihistamines, she started experiencing recurrent abdominal pain or laryngeal edema after the onset of the urticarial lesions, which responded only to C1 INH administration and were not controlled with methylprednisolone.

At routine follow-up, the patient's daily dose of tranexamic acid and levocetirizine was adjusted carefully according to her symptoms, and a good overall control of symptoms was managed with maintenance treatment and on-demand C1 INH.

There are only a few cases of coexistent HAE and CSU in medical literature.^{1–3} However, to the best of our knowledge, this is the first reported case with a clinical finding of a temporal-triggering effect of urticaria on bradykinin-mediated angioedema, which raises the interesting possibility of a pathophysiologic link between mast cell activation and bradykinin-mediated angioedema. Interestingly, the blockade of bradykinin receptors by icatibant (a 10–amino acid peptide analog of bradykinin) possibly activates mast cells,

resulting in an immediate hypersensitivity reaction in this patient. Consequently, bradykinin- and histamine-mediated mechanisms, the 2 distinct pathophysiologic mechanisms of angioedema, seem to trigger each other in this patient clinically.

It is traditionally believed that angioedema can occur either by mast cell activation mediators or bradykinin-mediated mechanisms as 2 distinct underlying disease processes.⁴ The classification of angioedema into 2 distinct groups in this regard facilitates our understanding of the underlying pathophysiology, and thus, enabling clinicians to diagnose and manage the patients better.⁵ Histaminergic angioedema can be considered within CSU and is managed with antihistamines and omalizumab in a stepwise approach, whereas bradykinin-mediated angioedema is responsive to C1 INH icatibant and kallikrein inhibitors, the drugs affecting kallikrein-kinin pathways.^{4,6}

The distinction between these 2 angioedema mechanisms was blurred by some experimental and clinical evidence indicating possible links between the 2 mechanisms. Mast cell heparin was previously found to activate the contact system and generate bradykinin in rodent models.⁷ In humans, initiation of contact system activation by activated mast cells resulting in bradykinin release was exhibited during anaphylaxis. Consequently, it was found that mast cell-driven heparin can trigger vascular leakage by factor XII-dependent bradykinin formation during anaphylaxis.⁸ A similar mechanism was recently found in symptomatic patients having CSU with the presence of elevated cleaved high-molecular-weight kininogen levels, reflecting increased bradykinin release in CSU compared with that of healthy controls. The cleaved high-molecular-weight kininogen levels normalized in patients during disease remission were not dependent on the presence of angioedema, acute angioedema attacks, or response to antihistamines; however, they were comparable with the levels detected in patients with HAE-1 and HAE-2, suggesting possible clinical relevance.⁹ These findings raise the possibility that mast cell activation-related allergic conditions may also involve the generation of bradykinin to some extent.

Besides the evidence of bradykinin generation in mast cell-related conditions, as a reciprocal relation, a triggering effect of bradykinin on histamine release from mast cells was also found in murine models and human skin mast cells.⁵ The recent clinical evidence of an immediate hypersensitivity reaction owing to icatibant, the bradykinin analog, is a good example of this possible relation. Icatibant was found to induce a local reaction on the injection site because of mediator release from activated mast cells, which can be reduced in severity by prophylactic administration of an H1-antihistamine.¹⁰ Although mast cell activation was assumed to be different from IgE-dependent activation, the positive skin test result of our patient increases the likelihood of an IgE-mediated mechanism.

Abdominal pain is typically thought of as a feature of bradykinin-mediated angioedema, but bradykinin- and histamine-mediated swellings are clinically indistinguishable. Moreover,

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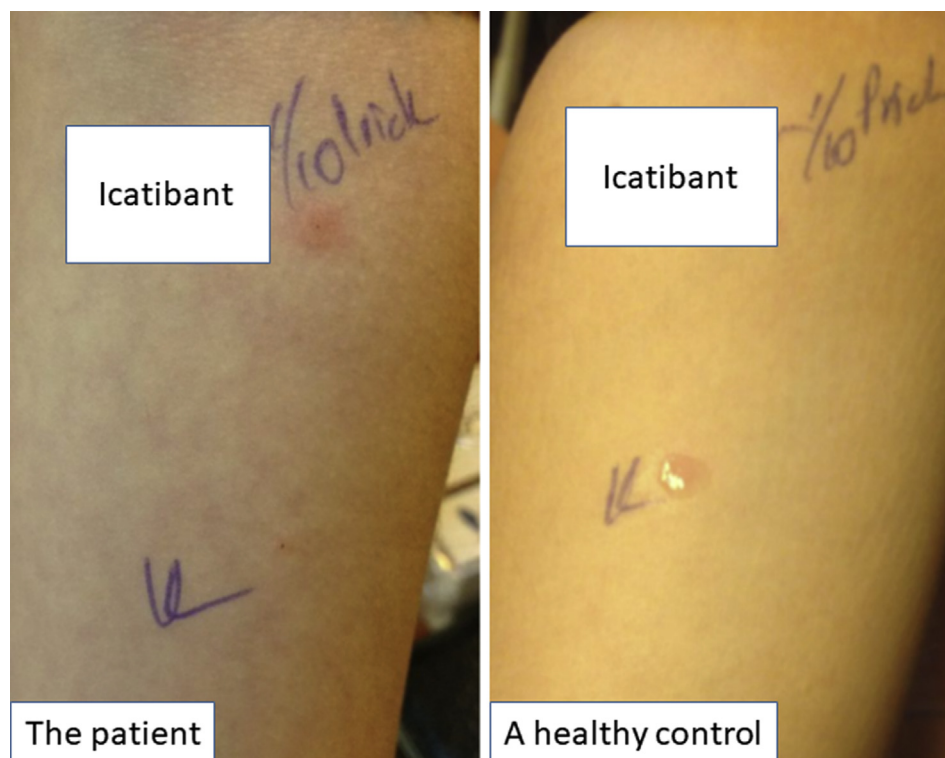


Figure 1. Positive skin prick test result of the patient with a 1:10 dilution of icatibant compared with negative skin prick test results in 5 other healthy subjects as control.

angioedema, which coincides with urticaria, is usually considered to occur as a result of mast cell activation and is traditionally considered as a feature of CSU. However, this case emphasizes the importance of obtaining a detailed history of the association between angioedema and urticaria regarding response to medications and changes our beliefs that mast cell activation and bradykinin release can together play a role in the clinical presentation of CSU and HAE. Mast cell activation triggering HAE seems to be a rare situation, and the underlying mechanisms need to be elucidated in further studies.

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References

1. van Kester M, Bergman W, Lavrijsen A. A female with hereditary angioedema developing wheals: a case report. *Acta Derm Venereol.* 2016;97(2):285–286.
2. Jorge AS, Dortas SD, Valle SO, Franca AT. Hereditary angioedema and chronic urticaria: is there a possible association? *J Investig Allergol Clin Immunol.* 2009;19(4):327–328.
3. Tadros S, Hayman GR. Chronic spontaneous urticaria and angioedema requiring treatment with omalizumab in a patient with hereditary angioedema. *Ann Allergy Asthma Immunol.* 2019;122(6):666–667.
4. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2017 revision and update. *Allergy.* 2018;73(8):1575–1596.
5. Zuraw BL, Christiansen SC. HAE pathophysiology and underlying mechanisms. *Clin Rev Allerg Immunol.* 2016;51(2):216–229.
6. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy.* 2018;73(7):1393–1414.
7. Oschatz C, Maas C, Lecher B, et al. Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. *Immunity.* 2011;34(2):258–268.
8. Sala-Cunill A, Björkqvist J, Senter R, et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. *J Allergy Clin Immunol.* 2015;135(4):1031–1043.
9. Hofman ZLM, van den Elzen MT, Kuijpers J, et al. Evidence for bradykinin release in chronic spontaneous urticaria. *Clin Exp Allergy.* 2020;50(3):343–351.
10. Maurer M, Church MK. Inflammatory skin responses induced by icatibant injection are mast cell mediated and attenuated by H(1)-antihistamines. *Exp Dermatol.* 2012;21(2):154–155.