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Letter to the Editor

## A case of cold-induced cholinergic urticaria accompanied by cholinergic urticaria showing a positive ice cube test

Dear Editor,

Cholinergic urticaria (CholU) is a frequent form of inducible urticaria provoked after sweating due to various stimuli that increase the core body temperature, such as exercise, hot bathing, emotional stress and thermal environment.<sup>1</sup> Its clinical features include itchy, pinpoint-sized wheals and surrounding erythema, and the symptoms are often worse in hot summer weather. Although the precise mechanisms are not completely understood, IgE-mediated mast cell activation and histamine release is extremely important in the pathogenesis of CholU. Patients with CholU frequently show an atopic background and have sweat allergy with specific IgE against a protein from *Malassezia globosa*, a major allergen contained in human sweat.<sup>2</sup> Cold-induced CholU is a rare phenomenon and is characterized by pruritic, small punctate wheals and flares after systemic cold exposure that are clinically indistinguishable from those of CholU.<sup>3</sup> Previous reports have shown that patients with cold-induced CholU present with wheals in areas both covered and uncovered by clothing after systemic cold challenge. We herein report a case of combined CholU and cold-induced CholU with positive ice cube test (ICT) results.

A 22-year-old woman presented with a 3-year history of the development of pruritic wheals during exercise, hot bathing and emotional stress. The symptoms worsened in summer, especially after sweating, and were sometimes associated with swelling of her bilateral eyelids. She had no episodes of anaphylactic reaction and was treated with H1 antagonists and an H2 antagonist by a primary dermatologist, but her symptoms were refractory. She also reported developing itchy punctate wheals after standing for a long while in the frozen-food section of the supermarket, where the room temperature was low, two months earlier. She had no history of cold contact urticaria. She was referred to our hospital for a further examination. Her medical history included mild atopic dermatitis and pediatric asthma.

A laboratory examination revealed a total serum IgE titer of 154.4 IU/ml. Her specific IgE antibody levels for *Malassezia* spp. were 3.11 UA/ml. Antinuclear antibody (1:160, homogeneous and speckled) and anti-thyroid peroxidase antibody (3.6 IU/ml, normal level <3 IU/ml) were positive, but levels of thyroid hormones were normal, and specific autoantibodies, including anti-DNA, anti-SM, anti-RNP and anti-SS-A/Ro autoantibody, were not detected. A test for cryoglobulins was negative. Treatment with antihistamines were discontinued, and a provocation test with sauna bathing (10 min at 70 °C, dry heat) induced swelling of her lips and bilateral

eyelids, erythema of the face and generalized pruritic wheals, followed by sweating (Fig. 1A). The wheals disappeared spontaneously within an hour. Results of a quantitative Sudomotor Axon Reflex Test revealed a normal sweating function, and cholinergic urticaria with acquired anhidrosis or hypohidrosis was denied. Intradermal injection of acetylcholine into the volar aspect of the forearm showed numerous pin-point hives around the injection site (Fig. 1B). In an autologous sweat skin test using her sweat collected during sauna bathing, the result was positive for 100-fold diluted sweat with wheal diameters of 6 × 7 mm accompanied by a flare reaction. The diagnosis of CholU with sweat hypersensitivity was therefore made.

She also complained of developing wheals in cold environments without any sweating stimulus. A systemic cold challenge test (sitting in a room at 4 °C for 7 min) was therefore performed. Five minutes after systemic cold exposure, pruritic small punctate wheals and surrounding erythema appeared in the cold-exposed areas, such as the face, forearms and back of her hands and feet, before spreading into areas covered by clothing (Fig. 2A, B). There were no associated systemic symptoms, such as fever or arthralgia, so cryopyrin-associated periodic syndrome was excluded. The plasma histamine levels 15 min after systemic cold exposure were elevated from 2.21 ng/ml to 5.65 ng/ml compared to before systemic cold exposure. She was diagnosed with combined CholU and cold-induced CholU. She was treated with 20 mg olopatadine hydrochloride, 10 mg levocetirizine hydrochloride and 40 mg famotidine.

The combination therapy was partially effective; no swelling of her eyelids and lips was observed, less pruritic wheals were induced after sweating, and pruritic punctate wheals were induced by systemic cold exposure mostly in cold-exposed areas. However, her quality of life was still significantly impaired, so treatment with 300 mg omalizumab was started. After the first administration of omalizumab, her symptoms promptly ameliorated. Omalizumab treatment was continued every four weeks and antihistamines were reduced gradually without exacerbation of her symptoms.

Cold-induced CholU, first described by Kaplan and Garofalo in 1981, is a subtype of chronic inducible urticaria (CIndU).<sup>3</sup> To date, there have been only nine published cases of cold-induced CholU.<sup>3–7</sup> Although the underlying causes are unknown, the involvement of histamine in the pathogenesis of cold-induced CholU is speculated, as elevations of plasma histamine levels after systemic cold exposure have been observed in some cases, including our own.<sup>1</sup>

Wanderer reported that a negative ICT result is one of the diagnostic features of cold-induced CholU.<sup>8</sup> Indeed, all of the published

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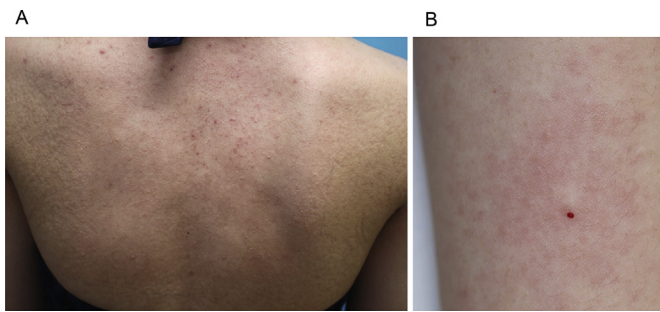


**Fig. 1.** (A) Generalized pruritic, small wheals developed after provocation test by sauna bathing. (B) Numerous pin-point hives surrounding the acetylcholine injection site.

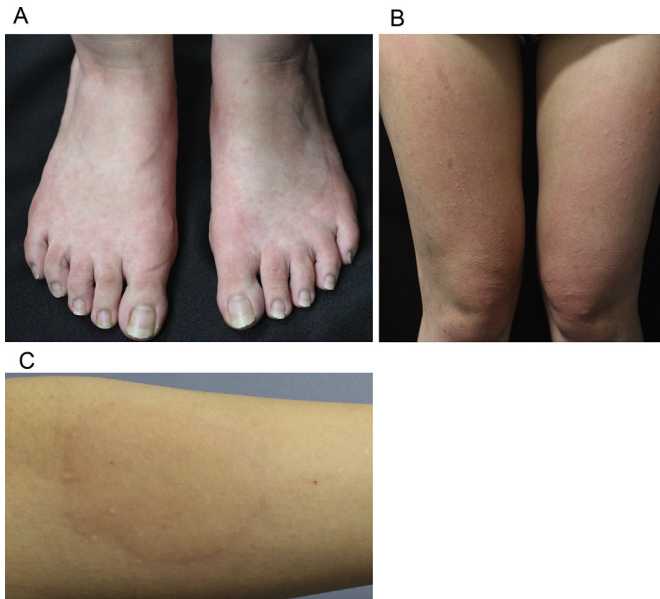


**Fig. 2.** (A–B) Pruritic small punctuate wheals appeared in both uncovered areas (A) and covered areas (B). (C) An ice cube test revealed an urticarial lesion at the challenge site.

cases except one were examined ICTs and showed negative results. Our patient also underwent an ICT, but the development of pruritus and urticaria was observed at the challenge site within 5 min after removing the cold stimulus (Fig. 2C). Our patient has not experienced cold contact urticaria (CCU) in her daily life, possibly due to her continued treatment with antihistamines, which suppressed the symptoms. To our knowledge, this is the first case of cold-induced CholU showing a positive ICT result. Asero reported that the autologous serum skin test (ASST) was positive in all five cases that were examined for CCU, and serum factors were speculated to be involved in the pathogenesis of CCU as both ICT and ASST became negative in two of the five cases after recovering from

the disease.<sup>9</sup> Our patient also showed a positive finding for ASST without any treatments. We hypothesized that CCU and cold-induced CholU might therefore have been independently associated in our case.

The management of CIndU is often challenging due to a poor response to antihistamines and difficulty avoiding the eliciting triggers, such as sweating and cold exposure. Recently, the recombinant humanized anti-IgE antibody omalizumab has been reported to induce a favorable response to refractory CIndU.<sup>10</sup> Our patient suffered from treatment-resistant CholU and cold-induced CholU for more than a year and decided to start omalizumab treatment, which resulted in complete symptom relief. Our findings suggest that omalizumab is an effective treatment not only for CholU but also for this rare form of CIndU, cold-induced CholU.

#### Conflict of interest

The authors have no conflict of interest to declare.

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