

## Letter to the Editor

# Combined cholinergic urticaria and cold-induced cholinergic urticaria with acquired idiopathic generalized anhidrosis



Dear Editor

Cholinergic urticaria (CU) was first described in 1924 by Duke.<sup>1</sup> It is characterized by pinpoint-sized, highly pruritic wheals with surrounding erythema that occur after sweating. In cold urticaria, patients experience pruritus and wheals within a few minutes after exposure to the cold. Idiopathic cold contact urticaria is the most common, whereas other types are rare. Cold-induced CU is an unusual disorder characterized by small punctate urticarial lesions induced by systemic cold challenge rather than the local cold challenge.<sup>2</sup> Some rare cases of combined CU and cold-induced CU have been reported.<sup>3,4</sup>

Acquired idiopathic generalized anhidrosis (AIGA) is a rare disorder with widespread loss of sweating caused by isolated failure of sympathetic sudomotor activity in the absence of other detectable abnormalities. AIGA is sometimes accompanied by CU. Here, we report the first case of combined CU and cold-induced CU accompanied with AIGA.

A 19-year-old female had a three-year history of the development of punctate wheals during physical exercise, bathing, emotional stress, and chilling of the body upon systemic exposure to the cold. She presented with eyelid oedema, lip oedema and dyspnea during sweating. In a previous medical facility, her symptoms were resistant to H<sub>1</sub> antagonists, H<sub>2</sub> antagonists and oral corticosteroids.

Laboratory tests demonstrated normal complete blood cell counts except for slight elevation of circulating eosinophils (7.6%) and normal biochemical findings except for total IgE levels (594.3 mg/dl). Normal levels of complement excluded hereditary angioedema. The patient also suffered discomfort, heat stroke and hypohidrosis in hot environments. She had to move house to avoid heat in the extremely hot and humid Japanese summer. CU was confirmed by the development of numerous small wheals and angioedema ≤15 min after an exercise test on a treadmill (Fig. 1A and B). Simultaneously, we tried to collect sweat from her forearm after exercise but no sweat was collected, suggesting that she had exhibited hypohidrosis. Her clinical history showed systemic exposure to cold induced punctate wheals similar to those seen in CU. Hence, a systemic cold challenge test (sitting in a room at 4 °C for 7 min) was undertaken.<sup>2</sup> Small punctate urticarial lesions with haloes were seen on areas covered by clothing, as well as under clothing uncovered after the test (Fig. 1C). Other accompanied symptoms such as fever and arthralgia were not observed, suggesting that familial cold autoinflammatory syndrome (cryopyrin-associated periodic syndrome) was excluded. Thus, she was diagnosed as having combined CU and cold-induced CU.

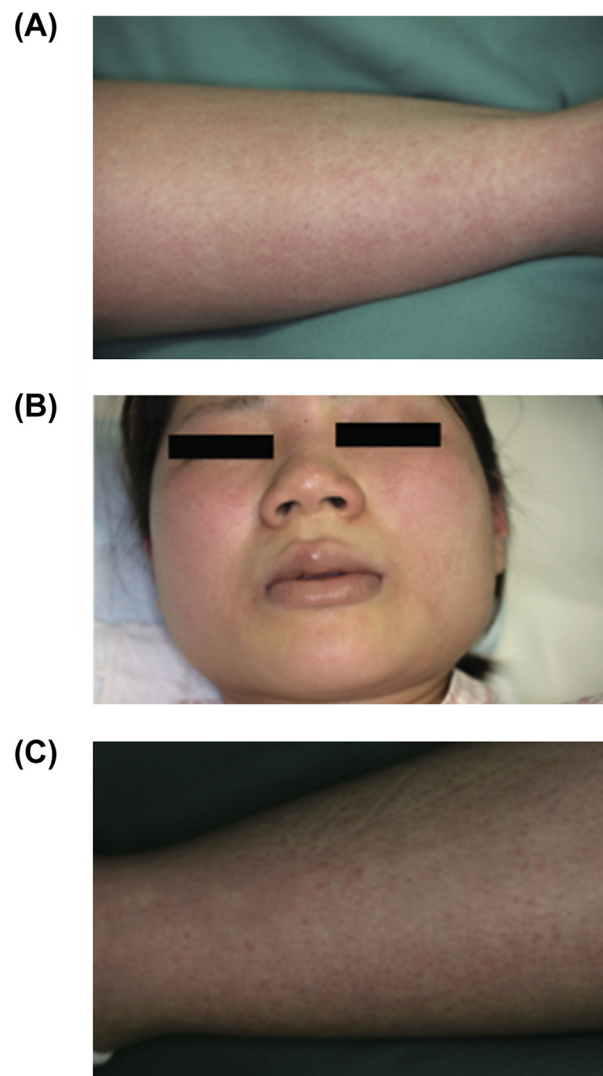


**Fig. 1.** Clinical images. (A) Numerous small wheals were produced after an exercise challenge test on a treadmill; (B) angioedema on the lip was observed after an exercise challenge test on a treadmill; (C) the systemic cold challenge test induced small punctate urticarial lesions with haloes in uncovered areas.

Peer review under responsibility of Japanese Society of Allergology.

<http://dx.doi.org/10.1016/j.alit.2014.12.004>

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Studies suggest that about two-thirds of CU patients have a strong allergy to autologous sweat and that half of CU cases show positive reactions in the autologous serum skin test.<sup>5,6</sup> Her autologous sweat was released in such small amounts that it could not be collected. Hence, allergy to sweat was evaluated by basophil histamine release tests with semi-purified sweat antigen (Allerport HRT®, Shionogi, Kyowa Medex, Japan).<sup>6</sup> The histamine release test using sweat showed a negative response and the autologous serum skin test exhibited a positive reaction. Next, we examined sweat function. A diagnosis of anhidrosis was assessed by a systemic thermoregulatory sweating test and local sweating test involving intradermal injection of acetylcholine and the starch–iodine (Minor) test.<sup>7</sup> The thermoregulatory sweating test showed almost generalized anhidrosis except for axillary zones (Fig. 2A). Intradermal injection of acetylcholine (100 µg/ml) produced no local sweating and satellite wheal (Fig. 2B). Histological findings revealed that morphological abnormalities of sweat glands and sweat ducts were absent, as was infiltration of lymphocytes around the sweat glands. Differential diagnoses for diseases involving hypohidrosis, such as Sjögren's syndrome and Fabry disease, were negative. Finally, she was diagnosed as having AIGA accompanied with combined CU and cold-induced CU.

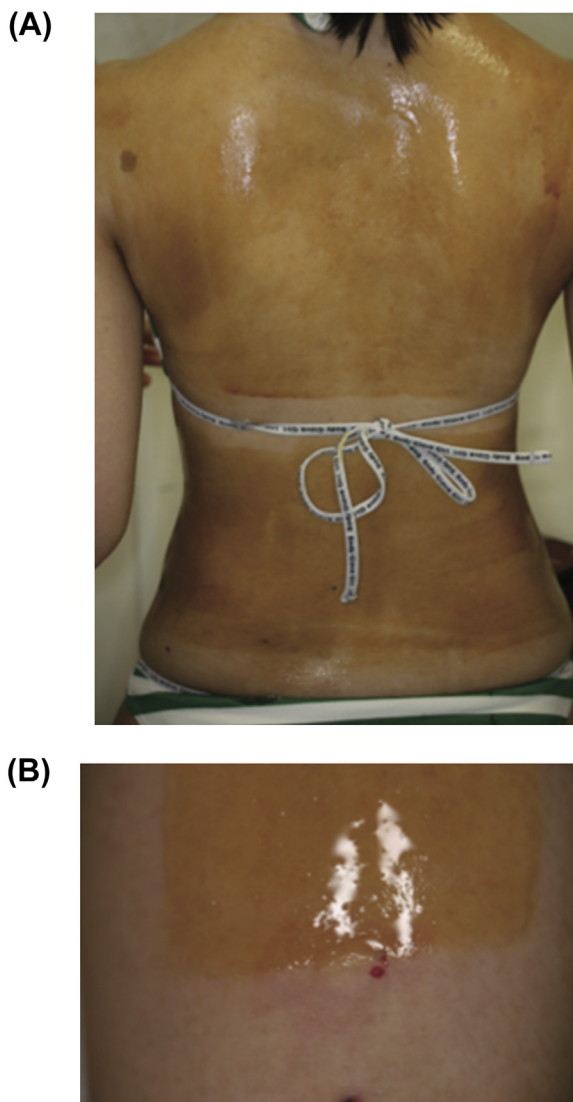


**Fig. 2.** Sweating tests using the iodine–starch method. (A) Thermoregulatory sweating test before corticosteroid treatment (almost no black-coloured dots on the back); (B) injection of acetylcholine produced no local sweating before corticosteroid treatment.

She complained most about heat stroke accompanied with hypohidrosis, so corticosteroid pulse therapy (CPT) using methylprednisolone (1000 mg/day for 3 days) was initiated. Two courses of pulse therapy improved sweating of the whole body except for the abdomen, heat stroke and CU without side effects, whereas symptoms of cold-induced CU were relieved slightly but prolonged. Then, intake of a combination of a H<sub>1</sub> antagonist and H<sub>2</sub> antagonist improved the symptoms of cold-induced CU gradually.

Before CPT, the punctate and highly pruritic wheals as well as heat stroke had a considerable impact on her daily life. After the diagnosis, her symptoms were improved by CPT. Following disappearance of heat stroke accompanied with improvement in hypohidrosis, CU symptoms were also relieved. This observation suggests that hypohidrosis and CU had a similar pathogenesis. Recently, Sawada et al. reported that reduced expression of cholinergic receptor M3 (CHRM3) and acetylcholine esterase could contribute to the pathogenesis of CU with hypohidrosis or anhidrosis.<sup>8</sup> It is possible that CPT improves expression of CHRM3 and acetylcholine esterase. In contrast, CPT could not completely relieve the symptoms of cold-induced CU. Reports suggest that some factors in serum contribute to the pathogenesis of cold urticaria,<sup>5,9</sup> so autologous serum factors in our patient might have been involved in the prolonged symptoms of cold-induced CU. However, further examination is necessary for the proof of more detailed pathogenesis in our patient.

#### Conflict of interest

The authors have no conflict of interest to declare.

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Received 22 October 2014

Received in revised form 8 December 2014

Accepted 14 December 2014

Available online 23 January 2015