Cholinergic Urticaria Associated with Acquired Hypohidrosis: An Ultrastructural Study

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Accepted August 20, 2010.

Cholinergic urticaria (CU) presents with a distinctive type of whealing: multiple small wheals or erythema characteristically appearing in association with sweating (1). Acetylcholine has been suspected to be the responsible mediator based on the cholinergic nerve regulation theory of sweating (2). This is supported by the fact that intradermal injection of cholinergic agents such as acetylcholine chloride produced satellite wheals, in some CU patients (1, 3). Recently, Kobayashi et al. (4) reported two cases of CU with acquired generalised hypohidrosis who displayed occlusion of the superficial acrosyringium, and postulated that leakage of sweat into the dermis leads to their development of wheals. Here we report a case of CU associated with hypohidrosis that appears, based on electron microscopic findings, to have been caused by hyperkeratinisation of the intraepidermal sweat duct epithelium.

CASE REPORT

A 33-year-old Japanese male firefighter with no history of atopic dermatitis was referred to our clinic. He had suffered from a pricking sensation and a rise in body temperature on cold days for 20 years. He sweated little on his trunk and extremities, even during exercise in hot environments. His symptoms disappeared during the summer months. His birth and development had been normal and he had suffered from no other diseases associated with hypohidrosis. His familial history was unremarkable.

CU was suspected from his repeated episodes of itchy wheals that appeared whenever his body temperature rose on cold days. An exercise provocation test, involving walking up and down stairs for 10 min, induced the formation of numerous wheals on his back, as well as a pricking sensation. The wheals disappeared one hour later. After increasing the exercise level so that it involved walking up and down stairs for 15 min at 28°, hypohidrosis was confirmed on the patient's back by the iodine-starch method. Sweating only occurred on the patient's palms and soles, axillae and foreneck; skin locations where no whealing was observed. Intradermal administration of 2 μg of acetylcholine chloride to his forearm induced the local formation of satellite wheals. A sweat test performed using the iodine-starch method further revealed anhidrosis in this area. During a separate visit, sweat was collected according to the methods described by Adachi & Aoki (5). After he had taken a bath, the skin of the patient's trunk was covered with wrapping film (Saran Wrap®, Asahi-Kasei, Tokyo, Japan) whose edges were then sealed with adhesive tape. After he had walked up and down stairs for 20 min, the film was removed from the patient's skin and the sweat that had collected on it was aspirated using a sterile injection syringe (Nipro, Osaka, Japan). We collected sweat not only from the patient's trunk, but also the axillae and foreneck, where sweating occurred normally. Sweat samples were sterile filtered using a 0.22 μm filter (Advantec, Tokyo, Japan) and subjected immediately to skin testing. Intradermal injection of 0.1 ml of the patient's sweat to the flexor surface of his forearm produced a wheal (7 × 6/28 × 30 mm) within 15 min. Histological examination of a biopsy specimen obtained from a wheal on his back, an area affected by hypohidrosis, exhibited upper luminal occlusion with keratinous materials and lower dilatation in the intraepidermal sweat ducts (Fig. 1). There was a lymphocytic infiltration around the sweat ducts in the upper dermis. These features were not observed in another specimen obtained from an area of skin that sweated normally (data not shown).

Ultrastructural examination of a specimen from an affected area of skin revealed luminal occlusion of intraepidermal sweat ducts caused by subcorneal accumulation of keratinous materials (Fig. 2). These keratinous materials were derived from the intraepidermal sweat duct epithelium since they were joined to each other by corneodesmosomes.

DISCUSSION

Our patient displayed occlusion of the upper parts of intraepidermal sweat ducts. This was not due to the dropping of segregated cornified cells from the surface of the epidermis into the lumens of the ducts. Instead, it seems to have been caused by hyperkeratinisation of the intraepidermal sweat duct epithelium, as supported by the observation that the keratinous materials present were attached to each other by corneodesmosomes. Our findings confirm those of a previous report concerning two CU patients (4), which suggested that occlusion of the superficial acrosyringium and subsequent leakage of sweat into the dermis led to the development of wheals. Rho (6) retrospectively reviewed the medical records of Korean soldiers with CU who visited his department between April 2001 and March 2006. The largest number of patient visits occurred in winter, peaking in December, and the fewest in summer, with a minimum in August, suggesting that dry skin is a risk factor for CU. Our patient also mostly complained of

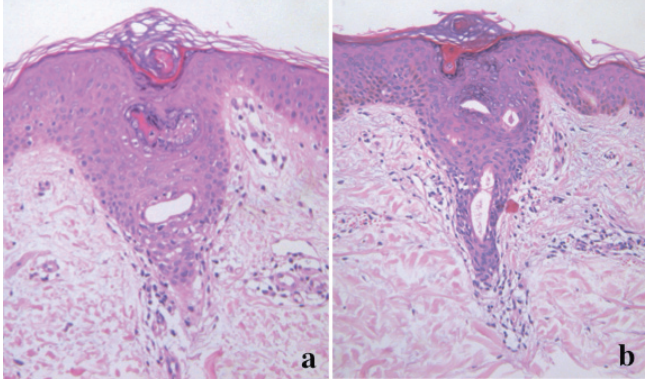

Fig. 1. Histological analysis of a biopsy sample taken from an area of dorsal skin affected by hypohidrosis. (a) Luminal occlusion of an intradermal sweat duct. (b) Lower dilatation of the same intradermal sweat duct.

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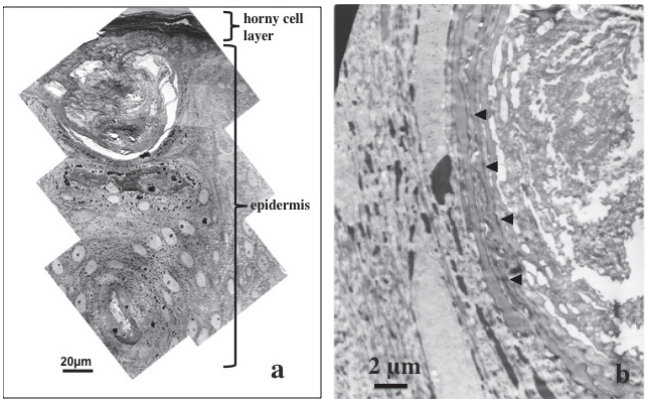

Fig. 2. Ultrastructural evaluation of hypohidrosis-affected skin. (a) Luminal occlusion of a sweat duct in the subcorneal region of the epidermis by keratinous materials. (b) Keratinous materials in this area attached to each other by corneodesmosomes.

his symptoms during winter, and never in summer. It is likely that patients with CU have a genetic predisposition to hyperkeratinisation of the intraepidermal sweat duct epithelium. Low temperatures and dry conditions during winter may enhance this process, resulting in occlusion of the acrosyringium. In summer, high temperatures and humidity may reduce hyperkeratinisation of the sweat ducts, thus causing urticarial reactions to cease. Serine protease activity in the human stratum corneum is higher during summer than in winter, which decreases local protein accumulation (7).

In view of the positive intradermal test with his sweat sample, we speculate that CU in this case developed due to leakage of sweat antigen into the surrounding dermis after occlusion of the intraepidermal sweat ducts, followed by mast cell activation via binding of surface IgE molecules to sweat antigen. This idea is supported by the report by Fukunaga et al. (8) that the majority of their patients with CU showed immediate hypersensitivity reactions to dermal injection of autologous sweat. Furthermore, Takahagi et al. (9) reported that sweat antigen induced the release of histamine from basophils of patients with CU associated with atopic diathesis. Interestingly, Hide et al. (10) reported that immediate skin hypersensitivity against sweat may be a common feature of atopic diseases regardless of disease severity, whereas skin tests with autologous sweat were positive in only 3 of 27 healthy volunteers (11.1%). We consider, therefore, that the positive skin prick test in the present case, who had no history of atopic disease, represented a specific reaction associated with CU.

Wallengren et al. (11) reported that substance P (SP) and vasoactive intestinal peptide (VIP) could cause a triple response, comprising local redness, flare and wheal, resembling urticarial lesions without sweating, in the tissue fluid of patients with factitious and cold urticaria. As we did not measure concentrations of SP and VIP, the possibility remains that these neuropeptides are involved in the whealing found in our patient.

Differential diagnosis includes miliaria profunda, whose pathogenesis involves occlusion of sweat ducts at the dermo-epidermal junction and intradermal sweat retention (12, 13).

It remains controversial whether intradermal injection of acetylcholine chloride produces wheals in patients with CU. Commens et al. (3) reported that only 25% of CU patients produced consistently positive responses to cholinergic agents in repeated intradermal testing. Patients with occlusion of the superficial acrosyringium may give positive test results if the agents used cause excessive sweating at the injection site, followed by the leakage of sweat into the surrounding dermis. The occlusion of intraepidermal sweat ducts may well explain the association of hypohidrosis with CU. However, the cause of hyperkeratinisation of the sweat duct epithelium requires clarification.

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