

CONCISE COMMUNICATION

Case of aquagenic urticaria: Case report and the results of histopathological examination

Maiko FUKAYAMA,¹ Yukako DOMOTO,² Shinichi SATO,¹ Yoshihide ASANO¹ 

Departments of ¹Dermatology, ²Pathology, University of Tokyo Graduate School of Medicine, Tokyo, Japan

ABSTRACT

Aquagenic urticaria (AU) is a rare skin condition in which dermal contact with water serves as a trigger of urticaria and pruritus. To make a diagnosis, a water challenge test is useful. We herein report a 16-year-old Japanese boy diagnosed with AU by water provocation test. The induced skin lesion histologically showed prominent degranulation of mast cells and lymphocytic infiltration throughout the dermis. This is the second report documenting the histopathological features of AU.

Key words: aquagenic urticaria, local cold urticaria, mast cell, osmolality, water challenge test.

INTRODUCTION

Aquagenic urticaria (AU) is a rare skin condition in which dermal contact with water at any temperature and from any source serves as a trigger of urticaria and pruritus. AU was initially described by Shelley and Rawnsley in 1964,¹ but has not been widely recognized, so that some patients seem to be misdiagnosed. The skin condition presents various symptoms of different sizes, including erythema, wheals or folliculocentric rash, mainly characterized by 1–3-mm folliculocentric, pruritic wheals with surrounding 1–3-cm erythematous flares. They develop within 20–30 min following skin contact with water, including the patient's own sweat and tears, then resolve within 1 h.^{1,2} To date, approximately 50 patients have been reported, of whom females tend to be more affected than males.² Few patients have showed additional systemic symptoms such as headache, lightheadedness, respiratory distress and palpitations.³ Most patients are likely sporadic, while there are several case reports of familial disease.² Diagnosis of AU is based on both a history of recurrent urticaria after water exposure and the positivity of a water challenge test. The pathogenesis of AU remains unknown, but it is likely mediated in histamine-dependent and -independent manners.⁴ We herein report a Japanese boy with AU and demonstrate its histological features. Written informed consent and institutional approval from the ethical committee of the University of Tokyo Graduate School of Medicine were obtained.

CASE REPORT

A healthy 16-year-old Japanese boy presented at our hospital due to a more than 2-year history of recurrent episodes of

erythema, wheals and pruritus that appeared on his shoulders, arms and trunk 5–10 min after water exposure. Water exposure included hand washing, rain, showering and even sweating, but he could drink water without symptoms. He generally experienced flat or slightly raised faint erythema up to 50 mm in diameter, but sometimes manifested soybean-sized pinkish wheals. The erythema or wheals often fused together into a relatively large rash, but he had never developed erythroderma. The symptoms lasted for 10–20 min, and then resolved spontaneously. There was no associated angioedema, hypotension or respiratory difficulty. No rash developed during mild exercise, but if he exercised hard and sweated, the symptoms appeared. He did not present dermatographism. His relatives had no similar histories.

Serological tests revealed elevated levels of immunoglobulin E (1965 IU/mL; normal, 0–170) and alkaline phosphatase (349 U/L; normal, 106–322). Eosinophil count and proportion and an immunological study were within normal ranges. We suspected him of having AU and decided to perform tolerance tests. After stopping antihistamines for a week, we initially performed a water provocation test. We divided his back into four parts, and placed towels impregnated with tap water, distilled water and 5% NaCl (dissolved in distilled water) without any pretreatment of the skin as well as a towel impregnated with 5% NaCl after complete removal of the stratum corneum with acetone (Fig. 1a); all four solutions were at room temperature (22–25°C). He complained of pruritus after 15 min at the sites of tap water and distilled water, especially accompanying edematous erythema on the latter area (Fig. 1b,c). In 20 min, relatively faint erythema was observed on the site of 5% NaCl without acetone pretreatment (Fig. 1d). All symptoms vanished within 20 min after the removal of the towels.

Correspondence: Yoshihide Asano, M.D., Ph.D., Department of Dermatology, University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: yasano-ky@umin.ac.jp
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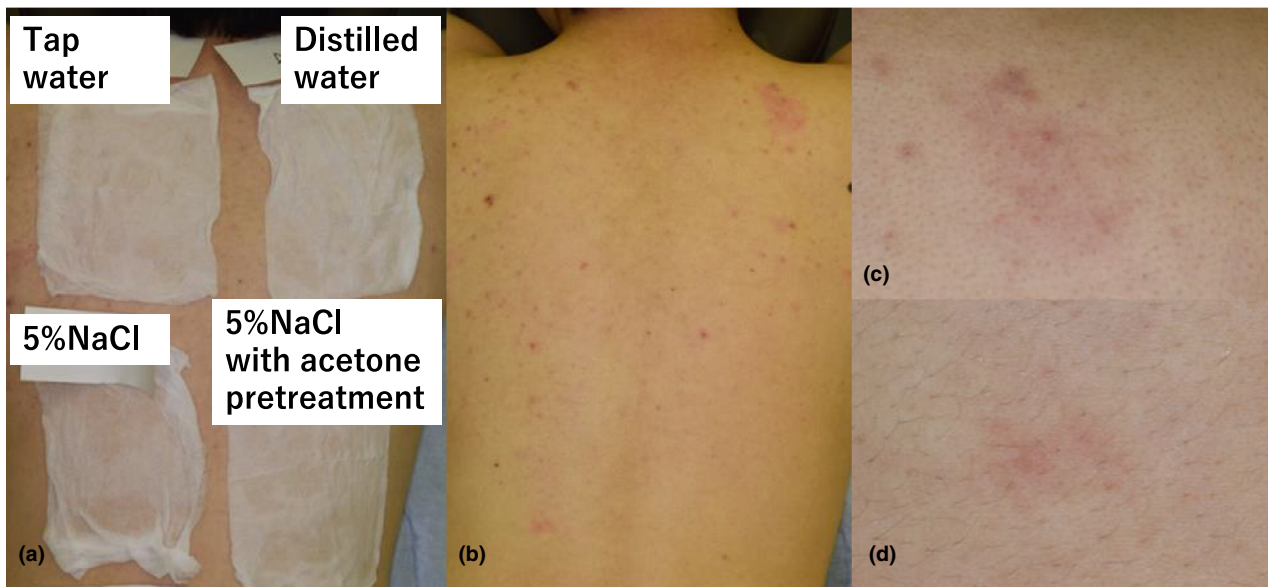


Figure 1. Water challenge test. (a) Wet towels were applied to the patient's back. (b) Results of water challenge test. (c) Edematous erythema was partially observed at the site of distilled water. (d) Faint erythema was observed partially at the site of 5% NaCl without acetone pretreatment.

To rule out other types of physical urticaria, we performed an ice cube test by exerting pressure upon a ice cube for 10 min on his right arm, showing a positive result (Fig. 2a). We also performed a local heat test by placing a beaker of hot water (40°C) on his left arm for 5 min, showing a negative result (Fig. 2b). He was further exposed to cold air (4°C) with and without exercise, but the exposure to cold air and exercise without sweating did not induce any skin rash. On the other hand, wheals and erythema were observed on the skin areas with sweating after exercise at room temperature. Based on these results, we diagnosed him as having AU and local cold urticaria. He was treated with levocetirizine hydrochloride (5 mg) and pregabalin capsule (75 mg) once daily, but their efficacy was limited.

A skin biopsy was obtained from the central areas of erythema induced by distilled water and ice cube, shortly after the removal of stimulation (within a couple of minutes). The

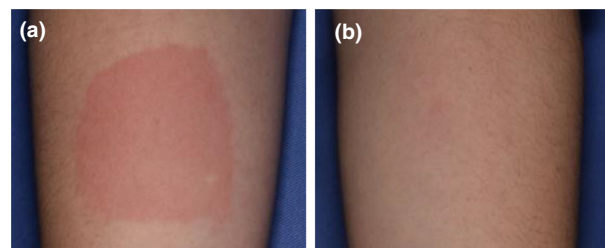


Figure 2. Ice cube and local heat tests. (a) Ice cube test showed obvious erythema. (b) Local heat test showed no change.

induced skin lesions displayed perivascular and periadnexal infiltration composed of lymphocytes and mast cells. There was no conspicuous interstitial edema. Immunohistochemical analysis of mast cell tryptase (MCT) using the VENTANA BenchMark automated staining system (Ventana Medical Systems, Tucson, AZ, USA) with I-VIEW DAB universal kit (Ventana Medical Systems) and anti-MCT antibody (M7052; Dako Japan, Kyoto, Japan) was performed according to the manufacturers' instructions. In the lesional skin of our patient, perivascular and periadnexal degranulation of mast cells were evident throughout the dermis, while the same staining procedure failed to detect degranulating mast cells in a control skin section obtained from the abdomen of a healthy volunteer (Fig. 3).

DISCUSSION

Aquagenic urticaria shares common manifestations and disease nature with other types of physical urticaria and aquagenic cutaneous disorders (e.g. cholinergic urticaria, cold urticaria, local heat urticaria, exercise-induced urticaria, localized salt-dependent AU and aquagenic pruritus).⁵ Cholinergic urticaria develops in response to cholinergic stimuli, such as exercising or stressful emotions. Cold urticaria, local heat urticaria and exercise-induced urticaria are the types of physical urticaria. Localized salt-dependent AU, a subtype of AU, is a condition with specificity for the salinity of water, patients with which develop urticaria after dermal contact with sea water, but do not or show less of a reaction with tap water.⁶ Aquagenic pruritus is characterized by intense pruritus and/or a stinging, tingling or burning sensation without any visible skin changes after water exposure.⁷ To make an accurate

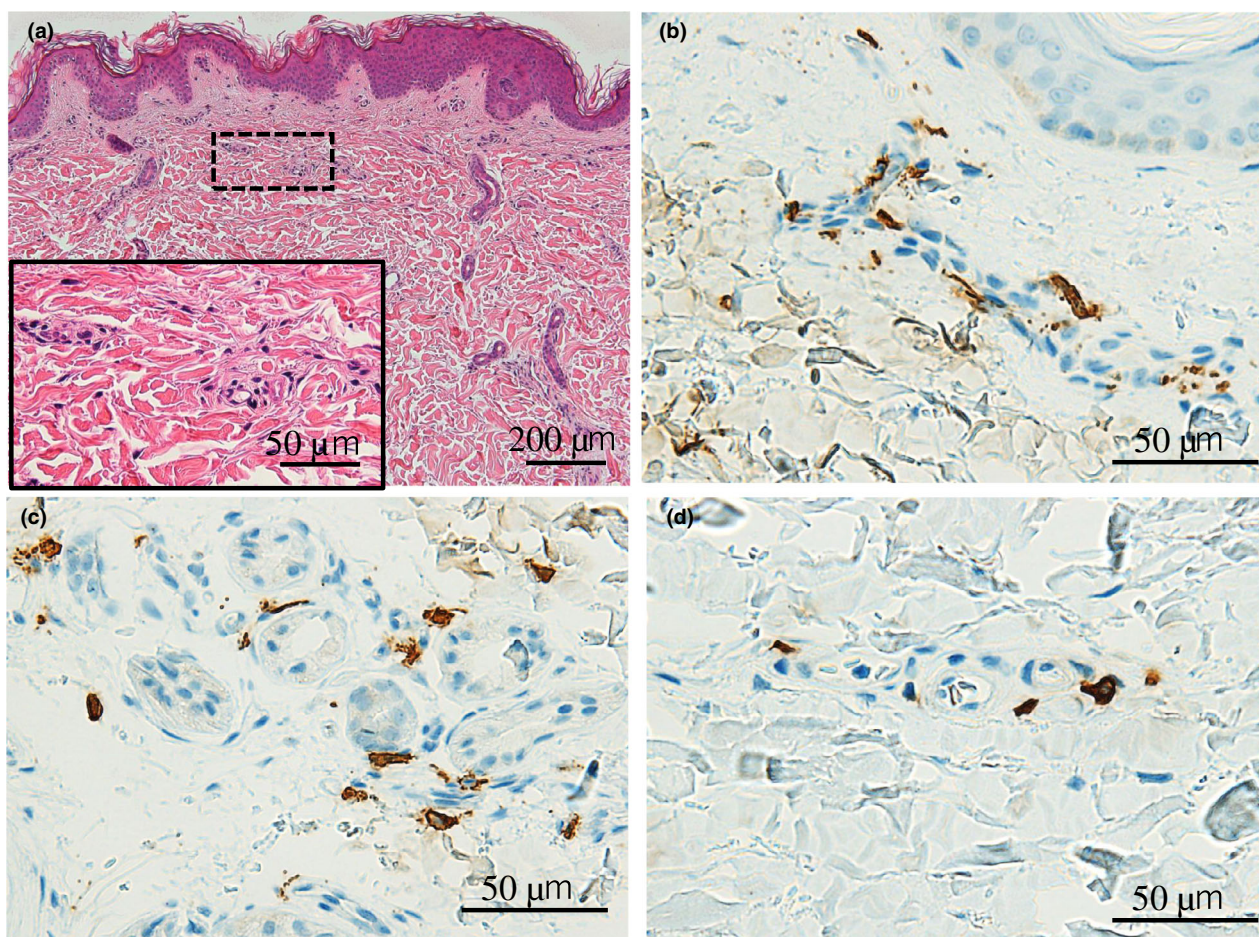


Figure 3. Immunostaining for mast cell tryptase. (a–c) Histological analysis of the distilled water-induced skin lesion. (a) Perivascular infiltration of lymphocytes (hematoxylin–eosin). The insert shows a higher magnification image of the region indicated by the dashed square. Prominent degranulation of mast cells was found in (b) superficial perivascular areas and (c) around periadnexal areas. Similar results were obtained in the ice cube-induced skin lesion. (d) Degranulation of mast cells was not observed in a skin section of a healthy control.

diagnosis, we conducted a series of provocation tests, such as water challenge, ice cube, local heat and exercise. We excluded aquagenic cutaneous disorders other than AU as well as other types of physical urticaria, except for local cold urticaria and cholinergic urticaria. Therefore, we diagnosed his symptoms as indicative of AU. Coexistence of local cold urticaria was suspected based on the result of the ice cube test, though he did not notice any clinical symptoms induced by cold exposure. Cholinergic urticaria could not be completely excluded without acetylcholine skin test because exercise can induce a similar skin rash in cholinergic urticaria and AU. However, skin rash was induced only after he sweated a lot, but not by exercise in a cold room, supporting the association of skin rash with water.

As a potential mechanism of AU, Shelley and Rawnsley¹ proposed that water reacts with a component in or on the stratum corneum, probably sebum, to produce a toxic compound which is absorbed and subsequently promotes discharge of

histamine from the perifollicular mast cells. Supporting this notion, Czarnetzki *et al.*⁷ demonstrated that soluble components of human callus extracted with Hanks' buffer reproduced a burning sensation in the skin of AU patients when locally injected, but not in controls, and induced *in vitro* histamine release from patients' peripheral blood basophils, but not from a healthy volunteer's. However, Sibbald *et al.*⁸ presented that complete removal of the stratum corneum with acetone enhanced the reaction to subsequent challenge by water, suggesting that AU development requires a close association between water and components in the epidermis or dermis. In our patient, of interest, acetone pretreatment suppressed the induction of wheals by 5% NaCl, suggesting that water-induced histamine release depends on components in or on the stratum corneum. Because distilled water induced a much greater skin reaction than tap water, some ingredients of tap water may weaken water-induced histamine release by somehow affecting the association of water with components in or

on the stratum corneum. Importantly, our case and that reported by Sibbald *et al.*⁸ shared common histological features in the water-challenged skin, such as mast cell degranulation without neutrophil and eosinophil infiltration and fibrin deposition. Therefore, the underlying pathogenic mechanisms are heterogeneous in AU, even though the final consequence of pathogenic responses, namely mast cell degranulation, is common. Further supporting the heterogeneity of AU, Sibbald *et al.*⁸ demonstrated the suppressive effect of locally applied scopolamine on water-provoked wheals, while Czarnetzki *et al.*⁷ failed to inhibit water-dependent wheal reaction by topically applied atropine.

Osmolarity may be another important factor involved in AU. In patients with salt-dependent AU, challenge tests with different hypertonic water solutions revealed that both salinity and hypertonicity may be pathogenically relevant.⁶ In our case, a wheal reaction to 5% NaCl (the concentration was determined according to a previous report)⁹ was weaker than that to distilled water and there was no pruritus in the NaCl-challenged skin. Therefore, the contribution of osmolarity to AU development seems to be also heterogeneous in individual cases.

In conclusion, we reported a case of AU diagnosed based on water provocation test. Because water is harmless for the majority, the potential association of skin eruption with water tends to be overlooked. Dermatologists should be aware of this rare clinical entity.

CONFLICT OF INTEREST: None declared.

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