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CASE REPORT

Aquagenic Urticaria Diagnosed by the Water Provocation Test and the Results of Histopathologic Examination

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An 18-year-old male visited our department complaining of recurrent episodes of an itchy rash after hand washing, showering/bathing, drinking water, and getting rain-soaked. He was diagnosed with aquagenic urticaria after a water provocation test and histopathologic examination. Five months of antihistamine treatment successfully prevented further wheal formation. Aquagenic urticaria is a very unusual form of physical urticaria caused by contact with water. It manifests as pruritic small wheals surrounded by erythema within 30 minutes of exposure. The condition can be diagnosed by a water provocation test. Systemic antihistamines are the first-line treatment, with anticholinergics, phototherapy, or barrier cream used alternatively or additionally. Four cases of aquagenic urticaria have been reported in Korea, but no histopathologic evaluation was reported in the English or Korean literature. Herein, we provide both a case report of aquagenic urticaria diagnosed by the water provocation test and histopathologic examination results for this patient. **(Ann Dermatol 29(3) 341～345, 2017)**

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INTRODUCTION

Aquagenic urticaria, first described in 1964 by Shelly and Rawnsley[1], is a rare variant of physical urticaria induced by direct contact with water, regardless of its temperature or source[2]. It is characterized by small punctate wheals on the area of skin in contact with the water[2]. Here we report a case of aquagenic urticaria during adolescence and review the clinical manifestations, pathogenesis, diagnosis, and current treatment modalities.

CASE REPORT

An 18-year-old male, with no previous medication, presented with a 1-week-history of recurrent erythema and small punctate wheals with pruritus. The lesions occurred 5～10 minutes after water exposure, including hand washing, dishwashing, getting rain-soaked, and showering/bathing, regardless of the water temperature or source, and were limited to the area of skin in contact with the water including face, neck, trunk, and both extremities. He also complained of pruritic erythematous changes, with swelling of the lips and oral cavity, after drinking water. Each episode lasted from 30 to 60 minutes and resolved spontaneously. He had no systemic reactions, such as headache or lightheadedness. Neither exercise nor cold exposure induced wheal formation. He had no personal history of allergies or atopic diseases nor a family history of similar reactions or lesions.

On physical examination, he demonstrated erythematous changes with pruritus on both hands after hand washing. A water provocation test was performed on his right arm using a towel soaked in tap water at body temperature. He complained of pruritus after 5 minutes, and multiple small wheals with surrounding erythema were observed on the

water-exposed area (Fig. 1). Stroking of the skin did not induce a wheal or flare reaction.

Laboratory tests revealed mild leukocytosis (11,030/mm^3), increased eosinophil cationic protein (48.2 μg/L), and increased total IgE (773 KU/L).

Histopathologic examination revealed conspicuous interstitial edema, a sparse perivascular and interstitial inflammatory infiltration composed of lymphocytes, mast cells, and a few neutrophils, and endothelial swelling (Fig. 2). An increase in the number of mast cells around the blood vessels was demonstrated by immunohistochemical analysis of c-kit (Fig. 3).

The patient was diagnosed with aquagenic urticaria and responded well to 20 mg bepotastine. He then received a prescription for 10 mg bepotastine once a day. At the 5-month follow-up, he did not report any further episodes of urticaria.

DISCUSSION

Aquagenic urticaria is a rare variant of physical urticaria[2]. It occurs predominantly in females, especially with the on-

Fig. 1. Multiple small wheals with surrounding erythema were seen on the right forearm after applying a towel soaked in tap water at body temperature for 5 minutes.

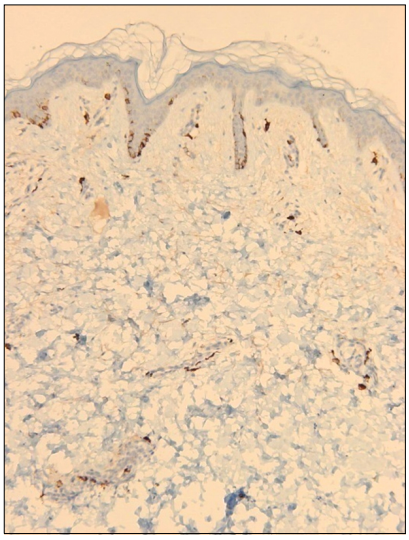

Fig. 3. Immunohistochemistry for c-kit showed slightly increased number of mast cells around blood vessels (×200).

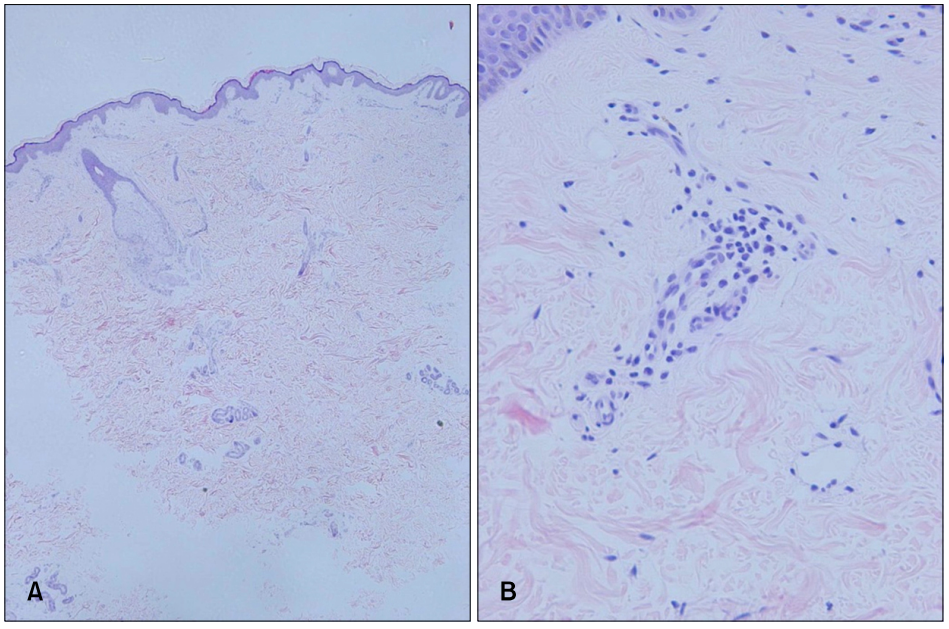

Fig. 2. (A) Histopathologic examination revealed conspicuous interstitial dermal edema and sparse perivascular and interstitial inflammatory cell infiltration (H&E, ×40). (B) A high-powered view showed perivascular infiltrate of lymphocytes and mast cells with endothelial swelling (H&E, ×400).

Table 1. Reported cases of aquagenic urticaria in the literature

No.	Sex	Age (yr)	Visit time from onset	Atopy or urticaria history	Family history	Biopsy	Successful treatment (time to remission)
1	F	27	18 yr	(−)	Brother	(−)	Avoidance (N/A)
2	F	24	2 yr	(−)	(−)	(−)	Avoidance (N/A)
3	M	49	3 yr	(−)	(−)	(−)	N/A
4[4]	F	30	1 yr	(−)	(−)	(−)	Promethazine, chlorpheniramine, hydroxyzine, petrolatum oint, scopolamine 9% sol (N/A)
5[4]	F	14	1.5 yr	(−)	(−)	(−)	Promethazine, chlorpheniramine, hydroxyzine, petrolatum oint, scopolamine 9% sol (N/A)
6[3]	F	29	15 yr	AC, AR, AU	Sisters	(−)	Terfenadine (N/A)
7[3]	F	17	2 yr		(−)	(−)	Terfenadine (N/A)
8[1]	F	15	N/A	(−)	(−)	(−)	Chlorpheniramine (N/A)
9[1]	F	17	4 yr	(−)	Father	(−)	N/A
10[1]	M	20	2.5 yr	Asthma, DG	(−)	(−)	N/A
11[6]	F	30	23 yr	DG	(−)	(−)	Clemastine 1 mg or tritoqualine 100 mg (N/A)
12[6]	F	40	33 yr	(−)	(−)	(−)	N/A
13	F	30	5 yr	(−)	(−)	(−)	Hydroxyzine 10 mg, cyproheptadine 4 mg (N/A)
14[8]	M	55	1 yr	DG	(−)	(−)	Hydroxyzine 25 mg (N/A)
15[13]	F	33	4 yr		Father	(−)	PUVA (2 wk)
16	M	3	<1 h	(−)	(−)	(−)	Dimetindene 15 drops (N/A)
17	F	21	3 yr	(−)	(−)	(−)	Astemizole 10 mg/d (N/A)
18[11]	M	7	2 mo	Asthma, AR, DG	(−)	(−)	UVB (22 wk), cyproheptadine 6 mg/d+hydroxyzine 75 mg/d (N/A)
19[7]	F	11	6 mo	ChU	(−)	(−)	Hydroxyzine 25 mg (1 wk)
20	M	29	6 mo	(−)	(−)	(−)	Hydroxyzine 20 mg (15 d)
21[10]	M	20	10 yr	(−)	(−)	(−)	Avoidance (N/A)
22[2]	M	17	10 mo	(−)	(−)	(−)	Desloratadine (9 mo)
23[2]	M	15	3 mo	(−)	(−)	(−)	Desloratadine (3 mo)
24	M	11	From baby	(−)	(−)	(−)	Hydroxyzine 50～75 mg/d (1 mo)
25	F	40	7 mo	(−)	(−)	(−)	Fexofenadine 360～540 mg/d (N/A)
26[12]	M	18	3 yr	(−)	Brother	(−)	Cetirizine 10 mg/d (N/A)
27[12]	M	18	3 yr	(−)	Brother	(−)	Cetirizine 10 mg/d (N/A)
28[14]	M	13	1 yr	(−)	(−)	(−)	Petrolatum cream (immediately)
29[15]	F	28	4 yr	(−)	Father, brother, sister, daughter	(−)	Refusal of treatment
30[15]*	F	1	From birth	(−)	See No. 29	(−)	Refusal of treatment
31	M	19	6 yr	(−)	(−)	(−)	Terfenadine 60 mg+mequitazine 6 mg+topical 1% diphenhidramine oint (partial improvement) (N/A)
32	F	21	2 yr	(−)	(−)	(−)	Levocetirizine 5 mg (N/A)
33[16]	F	21	1 mo	(−)	(−)	(−)	N/A
34[9]	F	36	1 mo	CoU	(−)	(−)	Treatment failure (hydroxyzine, chloropheniramine, cimetidine, prednisolone, mequtazine, cyproheptadine, montelukast, fexofenadine, petrolatum oint)
35[17]	M	19	3 yr	(−)	(−)	(−)	Fexofenadine 180 mg (2 wk)
36[17]	M	4	1 yr	(−)	(−)	(−)	Ketotifen syrup 10 ml (4 wk)
Our case	M	18	1 wk	(−)	(−)	Done	Bepotastine (5 mo)

F: female, N/A: not available, M: male, AC: allergic conjunctivitis, AR: allergic rhinitis, AU: acute urticaria, DG: dermographism, PUVA: psoralen plus ultraviolet A, UVB: ultraviolet B, ChU: cholinergic urticaria, CoU: cold urticarial. *A daughter of case No. 29.

set of puberty. Most cases are sporadic, but several familial cases have been reported[2]. Symptoms develop within 30 minutes after contact with water regardless of its temperature or source. The pruritic small wheals surrounded by erythema usually last less than 1 hour. Some patients report additional, systemic symptoms such as headache,

lightheadedness, respiratory distress, and palpitations, but these are usually rare[2].

The pathogenesis is still unclear, but the interaction of water with unknown components in the epidermis or dermis might cause histamine release from sensitized dermal mast cells, which in turn leads to wheal formation[1,3,4].

In addition to the patient's history, the diagnosis relies on the results of the water provocation test. Magerl et al.[5] (2009) recommended applying a wet cloth at body temperature onto an area of the skin for 20 minutes. Because aquagenic urticaria may be associated with other types of physical urticaria, such as dermographism, cholinergic urticaria, and cold urticaria[1,6-11], these condition should be excluded, especially cholinergic urticaria, in which the wheals are similar morphologically[2]. Previously reported cases of aquagenic urticaria are described in Table 1[1-17].

This patient was diagnosed with aquagenic urticaria based on his history, the results of a water provocation test, and a histopathologic examination, which showed interstitial dermal edema, endothelial swelling, and sparse infiltration of inflammatory cells, including mast cells around blood vessels.

Many of these histopathologic findings are the same as those of acute urticaria, in which interstitial dermal edema, dilated venules, endothelial swelling, and sparse infiltration of inflammatory cells have been described[18]. Mast cells are concentrated around the blood vessels of normal dermis, with one to three cells per cross-sectional vessel profile[19], but in this patient there were slightly increased numbers of mast cells around blood vessels.

Antihistamines are the first line treatment for aquagenic urticaria[12]. In recalcitrant cases, the dose can be increased by as much as four-fold the conventional dose[12]. Phototherapy and barrier cream are alternative or additional treatments if antihistamines fail to prevent recurrence[13]. The efficacy of phototherapy is related to its induction of both immunosuppression, including a decreased mast cell response, and epidermal thickening, which disturbs the penetration of water and thus also inhibits mast cell stimulation[10,20]. Barrier cream prevents the penetration of water into the dermis. However, the various emollients and water-resistant creams investigated have not yielded conspicuous success[14], except in a few cases in which a petrolatum-containing ointment was applied before water exposure[4,14]. Anticholinergics such as scopolamine may also offer relief[15]. Most of the patients were successfully controlled with antihistamines, although some of them changed treatment modalities because of drowsiness.

To the best of our knowledge, there have been only four cases[9,16,17] of aquagenic urticaria in Korea, but our case report is the first in the English and Korean literatures to include the results of the histopathologic examination.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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