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CASE REPORT

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Association of Cold Urticaria with Aquagenic Urticaria in an Adolescent Girl: A Case Report

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ABSTRACT

Physical urticaria is a heterogeneous group of inducible conditions in which symptoms are induced by exogenous physical triggers such as cold, water, heat, and mechanical stimuli, acting on the skin. Our case involves a sixteen-year-old female patient who presented with erythema, small wheals and pruritus on her skin after contact with water and cold. After conducting water and ice cube provocation tests in addition to her medical history and physical examination, the patient was diagnosed with aquagenic urticaria (AU) and cold urticaria (CU). Her complaints had started 20 days before presentation. Regardless of the temperature and the source of water, her symptoms increased after contact with water, and the physical examination disclosed thoracic scoliosis. Symptoms were significantly relieved after one month of antihistamine and liquid petrolatum treatment. However, the patient developed complaints of urticaria, itching and angioedema in the contact areas of the body after contact with cold air, cold water, and cold objects in the winter season. She was tested with ice cubes and the result was positive. We started treatment with omalizumab, and her symptoms improved at the eighth week of this treatment. Here we present an adolescent female patient diagnosed with CU and AU.

Keywords: Childhood, aquagenic urticaria, cold urticaria, antihistamine, omalizumab

INTRODUCTION

Aquagenic urticaria (AU) is a rare type of physical urticaria that occurs at any temperature after skin contact with water and less than 100 cases of AU have been reported in the literature (1-4). AU manifests in both men and women but is more frequently seen in women. Its occurrence is mostly sporadic, but familial cases have been reported (4,6). AU symptoms usually begin in adolescence, but childhood cases have also been reported (1-7). This disorder was previously identified in monozygotic twins (8). Cases with aquagenic urticaria have also been reported in our country (6,7,9). AU presents itself regardless of the temperature, source and pH value of the water, as well as the psychogenic factors. Municipal water, demineralized water, raw water and rainwater or even sweat can trigger AU symptoms (10,11). Typical lesions of 1-3 mm folliculocentric wheals surrounded by 1-3 cm erythematous flares may present, most frequently on the trunk and arms, and usually resolve spontaneously in 30 to 60 minutes (3,10,12,13). Systemic symptoms rarely develop, although, in some cases, symptoms such as wheezing and dysphagia have been reported. Uvula edema and dysphagia after drinking water have also been reported in some cases (3,14). Physicians may suspect AU based on the typical, recurring symptoms. Histopathologic examinations of AU lesions show nonspecific urticaria; for this reason, skin biopsies are not routinely recommended (1,2).

Cold urticaria (CU) is a physical urticaria characterized by the development of itchy wheals and/or angioedema after direct contact of the skin with cold air, liquids and/or objects. The affected person may also experience headache, palpitations, wheezing or fainting. There are two forms of the disorder: acquired CU and familial (hereditary) CU. Acquired CU is rare, affecting only about 0.05 % of the population. Acquired CU is further divided into two subgroups: primary acquired CU and secondary acquired CU. While primary acquired CU appears idiopathically, secondary acquired CU can be triggered by various chronic diseases (15,16). Here we report the case of an adolescent girl patient who has AU and CU.

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CASE REPORT

A sixteen-year-old female patient presented to our clinic with symptoms of erythema, small wheals and pruritus developing after skin contact with water. The complaints have started 20 days before admission. Regardless of water temperature or source, symptoms developed from hand washing and shower/baths. Symptoms occurred about 5-10 minutes after exposure to water, and the lesions were limited to the areas of skin contacting water. In addition, when the patient perspired, small wheals and pruritus developed on the skin areas in contact with the perspiration. The patient's skin symptoms were not accompanied by dyspnea, vomiting, abdominal pain, headache, or dizziness. In addition, the patient described pruritus in the oral cavity without systemic symptoms after drinking water. Each episode lasted 30 to 60 minutes and resolved spontaneously. The patient's complaints were not triggered by other physical factors, such as exercise, heat or pressure. Emotional stress, exercise and spicy food, known as triggers of cholinergic urticaria, did not trigger her symptoms. The patient's history revealed that there were no other chronic diseases, including allergic diseases. Moreover, there were no family members with similar complaints. There was a consanguineous marriage between the parents.

A physical examination was normal except thoracic scoliosis. Laboratory tests revealed the following: white blood cell count, 11.030 µL; hemoglobin, 13.6 g/dL; hematocrit, 38.1%; platelet count, 256000 µL; MPV, 9.3 fL; eosinophil count, 190 mm^3; and total immunoglobulin E (IgE), 111 IU/mL. In addition, coagulation parameters, biochemical tests, urine assay, immunoglobulin levels, thyroid function tests and autoantibodies, hepatitis markers, C3, C4, CH50, antinuclear antibodies, serum tryptase, rheumatoid factor, and cryoglobulins were within normal limits. Bacterial, viral and protozoal infection tests were negative, and a skin prick test showed no sensitization.

X-rays revealed thoracic scoliosis with convexity to the right (Figure 1). The patient was consulted to the orthopedics department; idiopathic scoliosis was diagnosed and exercise therapy was recommended. A water provocation test was conducted on the patient's forearm by applying a soaked towel at 35°C for 30 minutes. The patient reported pruritus at the test site within 5-10 minutes, and erythema and urticarial lesions were found at the contact site (Figures 2A,B). Similar symptoms developed in provocation tests with tap water and distilled water. A provocation test with salt water was also positive; however, the skin findings in this test were milder than the one with normal water. The patient was also tested with ice cubes and the test was positive. As a result of the above tests, the patient was diagnosed with primary acquired CU (Figures 2C,D). Dermographism, pressure, and exercise tests were performed to rule out other physical urticaria types; no skin lesions were observed after these tests.

Written informed consent was obtained from the parents of the patient.

DISCUSSION

A sixteen-year-old female patient presented with erythema, small wheals and pruritus on her skin after contact with water and cold. Several forms of physical urticaria can coexist in the same patient, and some observations report the association of AU-dermographism and AU-cholinergic urticaria. However, the coexistence of AU and acquired CU in the same patient is very rare. Mathelier-Fusade et al. reported the association of CU and AU in a 27-year-old woman for the first time (17).

In order to define the genetics of AU and CU, investigating their relationship with other diseases is recommended. AU has rarely been associated with other diseases. In the literature, associations with rhinitis, asthma, migraine, lactose intolerance, HIV infection, Bernard-Soulier syndrome, and occult papillary carcinoma have been reported (4,9,10,18). In our patient, we detected only scoliosis, an association that might be random. To the

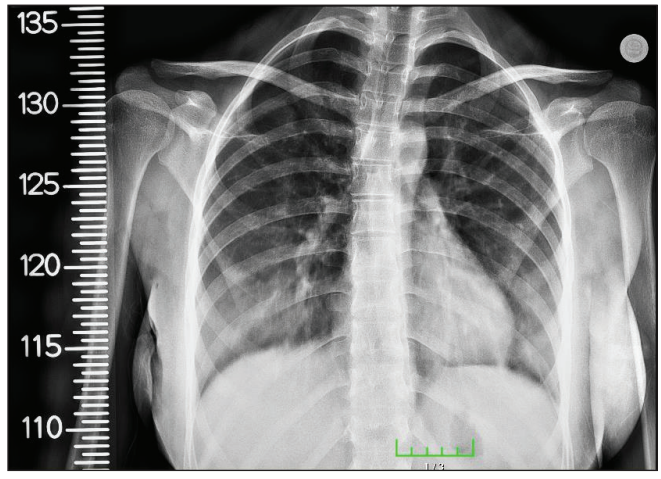

Figure 1. Scoliosis image on the patient's chest X-ray.

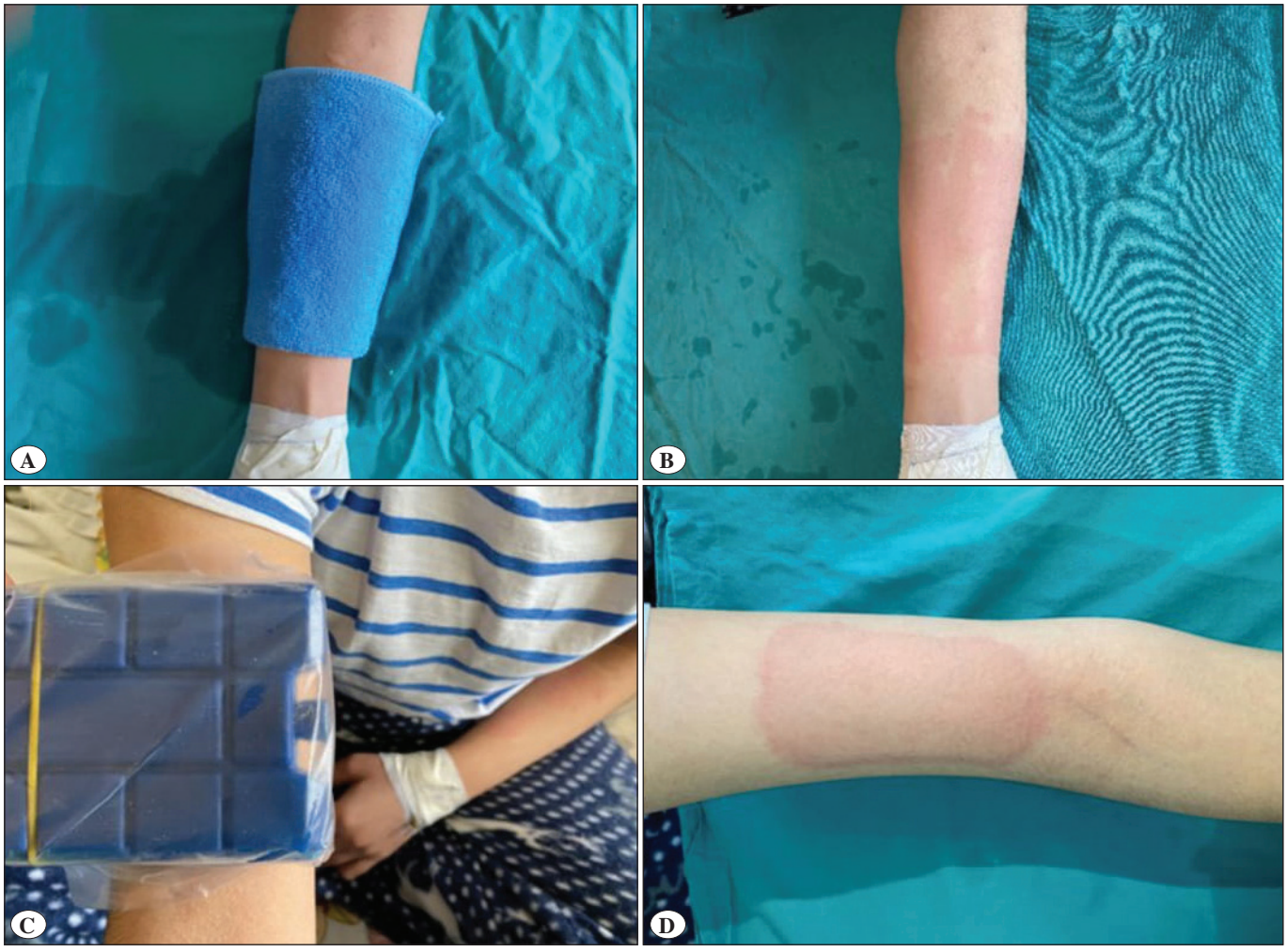

Figure 2: A,B: The erythema and wheals on the forearm after water provocation test; C,D: The erythema and wheals on the forearm after the ice cube provocation test.

best of our knowledge, our patient is the first case in the literature with AU and CU accompanied with scoliosis.

The pathogenesis of AU is not fully known. However, several mechanisms have been proposed. It is thought that water interacts with sebum or sebaceous glands and then acts as an intermediary for transporting epidermal components (antigens) to the dermis that develop into urticarial lesions due to histamine release (14). However, Luong and Nguyen found that, in some patients, the expected increase in histamine level of the water provocation test was not triggered (3). Acetylcholine and methacholine are other chemical mediators considered for the pathogenesis of AU. Sibbald et al. observed that the administration of local scopolamine (an acetylcholine antagonist) on the skin of AU patients before contact with water suppressed urticaria and erythema formation. In the light of these data, the authors proposed a mechanism that could be independent of histamine release (19). However, another study failed to reproduce this finding when pretreatment with atropine did not result in the suppression of subsequent wheal formation (14). In addition, methacholine injection testing is negative in patients with AU; however, it is often positive in cholinergic urticaria (10). Furthermore, Tkach hypothesized that hypotonic water sources could lead to osmotic pressure changes, that a sudden change in osmotic pressure around hair follicles may lead to increased passive diffusion of water resulting in the indirect provocation of urticaria (20). Later, they described cases of AU due to a decrease in the thickness of the stratum corneum after epilation that supported Tkach's hypothesis (3,21).

It has been reported that some AU patients may develop itchy urticarial lesions from body fluids such as sweat, saliva and tears (10). When our patient was sweating, wheals and pruritus were seen in the body areas that came into contact with sweat, but her condition was not severe enough as that induced by water. Reactions of AU to saline are variable. Some AU cases react to tap water and sweat, yet can swim in the ocean without developing urticaria. In contrast, cases of AU due to saline have been reported (2,21). In our patient, the provocation test results with saline were similar to those with tap water.

In general, the first line treatment for AU is second-generation H1 antihistamines (1,14). In addition to or as an alternative to these antihistamines, first-generation H1 antihistamines, H2-receptor antagonists, barrier-forming creams (oil-in-water emulsion and petrolatum containing creams), acetylcholine antagonists, stanozolol, fluoxetine, phototherapy (including psoralens ultraviolet radiation A and ultraviolet radiation B), and omalizumab can be administered (2,3,10,14,19). Our patient was started on an oral antihistamine, the daily dose of which was quadrupled. In addition, the patient was advised to apply liquid petrolatum to the skin before contact with water. After one month of antihistamine treatment, the patient's complaints after contact with water disappeared.

However, the patient developed complaints of urticaria, itching and angioedema in the contact areas of the body after contact with cold air, cold water, and cold objects during the winter season. An ice cube-filled plastic bag was applied to the patient. The test was positive. In contrast, the patient's forearm was administered the water provocation test with a soaked towel at 35°C and the result was negative. We started treatment with 300 mg omalizumab by subcutaneous injection every four weeks, and the symptoms of CU improved in the eighth week of this treatment. The patient's CU symptoms did not respond to antihistamine therapy, but responded to omalizumab therapy. In the light of these results, we speculate that there are various secreted mediators in both AU and CU. The pathogenesis of CU is not yet fully understood, but it is likely to involve IgE-mediated mast cell activation. It has also been proposed that it could be related to mast cell degranulation and the release of histamines, as well as various inflammatory mediators (15,16). The response to omalizumab treatment in our case supports these mechanisms.

CONCLUSION

Here we report a case of an adolescent girl with AU, CU and scoliosis. Although clinical manifestations and diagnostic procedures for AU and CU have been established, more research is needed to define their pathogenesis. The data from these studies will help us develop effective therapies for AU and CU.

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