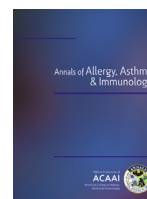




ELSEVIER

Contents lists available at ScienceDirect



Letter

Rhabdomyolysis-induced transient cold urticaria

Acquired cold urticaria is a subtype of physical urticaria and is characterized by the development of wheals and/or angioedema after exposure to cold stimuli.¹ These symptoms are usually self-limiting but can be life-threatening, especially with an anaphylactic reaction from extensive cold contact during aquatic activity or pharyngeal angioedema after consuming cold food or beverages.² Acquired cold urticaria can be classified into primary and secondary forms. Most cases are primary; the secondary form is rare. Various causes have been reported to be associated with the secondary form, including cryoglobulinemia, cryofibrinogen, cold agglutinin, cold hemolysin, malignancies, leukocytoclastic vasculitis, and infectious diseases.¹

We report a case of transient cold urticaria, induced by rhabdomyolysis, which developed 2 days after strenuous exercise and lasted for 1 week. Rhabdomyolysis-induced cold urticaria has not been reported previously.

In late April, a 38-year-old Japanese man undertook weight training at the gym; 2 days later, he developed painful and pruritic generalized swelling and erythema on the skin after being exposed to cold stimuli, including cold air, water, and objects. The affected skin returned to normal within 1 hour when warmed up. He presented to our clinic on the day of onset. On physical examination, he had painful swelling and erythema symmetrically on both hands and ears (Fig 1). He stated that his face also had been swollen and reddish, but that it had started to resolve shortly after he arrived at the clinic and had disappeared before he saw a physician. All these skin lesions had developed while he was walking outside from his office to the clinic in the cold air. He also had modest muscle aches over the anterior chest and arms, comparable to delayed-onset muscle soreness and likely caused by his recent weight training; otherwise he was asymptomatic.

He did not have any urticaria during or after the weight training until 2 days later. He did not develop any urticarial reactions to heat, hot water, water, sweat, or exercise, but only to cold stimuli. The urticaria he had was diffuse and generalized in nature and had developed only on the skin areas exposed to cold stimuli. He denied developing any cholinergic urticaria-type small punctate wheals or hives.

Laboratory testing showed markedly elevated levels of creatine kinase (11,489 IU/L, reference 30–200 IU/L), consisting of 100% MM fraction and elevated lactate dehydrogenase (719 IU/L, reference 125–243 IU/L), aspartate aminotransferase (102 IU/L, reference 5–45 IU/L), and IgE (358 kU/L, reference 0–100 kU/L). Antinuclear antibodies were weakly positive with speckle patterns. Test results for cryoglobulin, cryofibrinogen, rheumatoid factor, CH50, C3, C4, C1 esterase inhibitor, anti-SS-A, SS-B, Smith, ribonuclear protein, Scl-70 and Jo-1 antibodies, rapid plasma reagin, hepatitis B and C panels, C-reactive protein, erythrocyte sedimentation rate, white

blood cell count and its differential, thyrotropin, free triiodothyronine, and free thyroxine were unremarkable. Histamine and potassium levels were normal at 358 nmol/L and 4.8 mmol/L, respectively.

An ice cube test produced a positive reaction. The patient was started on 120 mg of fexofenadine once daily and 150 mg of nizatidine twice daily, and then fexofenadine was replaced with 1 mg of ketotifen twice daily, but neither regimen alleviated his symptoms. He had experienced cold urticaria for only 1 week, during which the severity of cold urticaria gradually tapered off as muscle soreness decreased. When he returned for a follow-up visit 9 days after onset, he was completely asymptomatic and had no urticaria, even after further exposure to cold stimuli. A repeated ice cube test produced a negative reaction. The laboratory tests showed that the creatine kinase level had almost normalized (210 IU/L), and previously elevated levels of lactate dehydrogenase and aspartate aminotransferase were within normal ranges.

The patient was a graduate-school student living in London. His medical history was significant for on-and-off pompholyx eczema of the hands and soles of the feet since 14 years of age. He was taking no medication. He denied any medical and family history of atopic dermatitis, asthma, autoimmune diseases, or allergies. He admitted that he had previously had an identical episode of delayed-onset exercise-induced cold urticaria 1.5 years previously in October, just like the current episode, only over the course of several days after weight training. He neither underwent weight training nor developed cold urticaria between these episodes. Light exercise did not cause any urticaria.

This patient had cold urticaria transiently for 1 week, commencing 2 days after strenuous exercise. It was speculated that cold urticaria was induced by rhabdomyolysis, because the patient had cold urticaria and a positive ice cube test reaction corresponding to the period indicating elevated creatine kinase and muscle ache, and the severity of cold urticaria was related to the degree of creatine kinase elevation and muscle ache. This was supported by the fact that 1.5 years previously he developed an identical episode of cold urticaria after weight training.

Cold urticaria can coexist with other types of physical urticaria, and one can argue that this case features cold and cholinergic urticaria.³ However, exercise, heat, and sweat did not cause the present case of urticaria. Another possibility is that exercise lowered the threshold for urticaria. This seems unlikely because the cold urticaria episodes developed a few days after strenuous exercise, when muscle ache started and creatine kinase was elevated, not during or right after the exercise. In addition, light exercise did not cause any urticaria in this patient.

The underlying mechanisms of cold urticaria are not fully understood, but it is postulated that mast cells, when activated by anti-IgE autoantibodies along with cold stimuli, release histamine and other inflammatory mediators such as tumor necrosis factor- α

Disclosure: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2014.08.005>

1081-1206/© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.



Figure 1. Painful and pruritic swelling and erythema on the hands and ears developed after walking outside in the cold air when the patient was having cold urticaria.

or interleukin (IL)-3.^{1,4–6} Strenuous exercise, especially eccentric exercise, causes muscle damage and delayed-onset muscle soreness.⁷ The damaged muscle tissues activate inflammation, which induces an increase in circulating inflammatory mediators, including tumor necrosis factor- α , IL-1, and IL-6.⁸ In particular, serum IL-6 level is substantially increased over a few days after eccentric exercise and is significantly correlated to creatine kinase levels.⁷ In the present case, given the fact that severity of cold urticaria was related to the degree of muscle ache and to creatine kinase levels, some of these inflammatory cytokines may have played an important role in the development of transient cold urticaria.

Acknowledgments

The authors gratefully acknowledge Kumiko Tanaka, RN, Asami Suzuki, RN, and Hanae Chandee, RN, at the Department of Nursing, Japan Green Medical Centre, for their generous assistance and technical support.

Gotaro Kojima, MD
Katsunori Ishida, MD, PhD
Yasuhiro Takashima, MD, PhD
Hitoshi Kurata, MD, PhD

Ryuichiro Sasae, MD
Yoshihiro Takaya, MD, PhD
Japan Green Medical Centre
London, United Kingdom
gotarokojima@yahoo.co.jp

References

- [1] Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis, and management. *J Allergy Clin Immunol*. 1990;85:965–981.
- [2] Siebenhaar F, Weller K, Mlynec A, et al. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. *Clin Exp Dermatol*. 2007;32:241–245.
- [3] Sigler RW, Levinson AI, Evans R III, Horakova Z, Kaplan AP. Evaluation of a patient with cold and cholinergic urticaria. *J Allergy Clin Immunol*. 1979;63:35–38.
- [4] Krause K, Zuberbier T, Maurer M. Modern approaches to the diagnosis and treatment of cold contact urticaria. *Curr Allergy Asthma Rep*. 2010;10:243–249.
- [5] Hermes B, Prochazka AK, Haas N, Jurgovsky K, Sticherling M, Henz BM. Upregulation of TNF- α and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol*. 1999;103:307–314.
- [6] Tillie-Leblond I, Gosset P, Janin A, et al. Tumor necrosis factor- α release during systemic reaction in cold urticaria. *J Allergy Clin Immunol*. 1994;93:501–509.
- [7] Tomiya A, Aizawa T, Nagatomi R, Sensui H, Kokubun S. Myofibers express IL-6 after eccentric exercise. *Am J Sports Med*. 2004;32:503–508.
- [8] Pedersen BK, Ostrowski K, Rohde T, Bruunsgaard H. The cytokine response to strenuous exercise. *Can J Physiol Pharmacol*. 1998;76:505–511.