Cold Urticaria With an Unusual Response to Cold Stimulation Test

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ABSTRACT

Urticaria is a transient and pruritic cutaneous condition that can be caused by a multitude of triggers. Mast cell release of histamine and other cytokines is the unifying pathophysiology of these triggers. Cold urticaria is a self-limited disease in which low temperatures may instigate these skin lesions. It is typically diagnosed with a positive cold stimulation test (CST), which is defined as showing a palpable and clearly visible wheal-and-flare skin reaction at the test site upon rewarming after cold exposure with an ice cube.

We present the case of an 18-year-old Caucasian female who presented with a 6-month history of hives brought on by cold temperatures and alleviated with rewarming and antihistamines. She did not have any urticarial lesions on examination, but upon a cold stimulation test, she

developed urticaria at sites distant to ice cube placement. She was diagnosed with idiopathic cold urticaria, and prophylactic cetirizine was recommended, along with additional diphenhydramine for breakthrough lesions. She was also provided with a prescription for epinephrine auto-injectors and instructed to avoid cold immersion given the risk of anaphylaxis.

Cold urticaria is a disease that may have systemic consequences and can be diagnosed with a thorough history and a noninvasive CST. This test provides the stimulus for mast cell degranulation, but the phenomenon of this occurring at a site remote to where the stimulus was placed is not well described in the literature. Given the consequences of undiagnosed cold urticaria, this patient's case could impact how this test is performed and assessed.

Introduction

Urticaria, more commonly known as hives, is an extremely common

medical disorder, experienced by up to 20% of the population.¹ These pruritic and transient

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cutaneous lesions are the result of histamine and cytokine release, causing vasodilation and leakage of fluid into the dermis. Mast cells, which release these inflammatory mediators, may be activated by multiple mechanisms, including direct activation by antigens or other stimuli, as well as IgE-mediated receptor cross-linking. Malignant etiologies such as vasculitis and malignancy may be underlying stimuli for urticaria, but the vast majority of cases are attributed to triggers such as infection, insect bites, and allergen exposure. While not as common, physical stimuli including pressure, vibration, and temperature extremes may also induce mast cells to release histamine.

As the name implies, cold urticaria results from mast cell degranulation following cold exposure.² It is typically diagnosed with a positive cold stimulation test (CST), which is defined as the development of a palpable and visible wheal-and-flare skin reaction at the test site upon rewarming following cold exposure with an ice cube. This disorder most frequently affects young adults (mean age of onset of 25 years³) and is typically self-limiting over the course of years (mean time to resolution 5.6 years⁴). We report the case of this disease in a young Caucasian woman with an unusual finding on physical exam in which she developed urticaria in sites remote to cold stimulation. This may suggest that clinicians suspecting cold urticaria should assess the patient thoroughly following the CST, beyond just the forearm on which the ice cube is placed.

Case Presentation

An 18-year-old Caucasian female with a history of celiac disease presented to the University of Michigan Allergy Clinic for evaluation of an intermittent rash of 6 months duration, for which she had not previously seen a provider. She did not have the rash at the time of the visit but believed that it was hives. This was corroborated by her description of the lesions as intensely pruritic, arising within 10-15 minutes of exposure to cold temperatures, and improving within an hour after rewarming.

With diphenhydramine, symptoms improved within 10-20 minutes. She reported that she had recently visited Lake Michigan but had declined to go in the 56-degree water due to her suspicion of cold temperatures causing her symptoms. She denied constitutional symptoms or a recent history of infection. Family history was noncontributory but could not be fully assessed as both parents were adopted.

On examination, the patient's skin was clear and urticaria-free. A cold stimulation test was performed by placing an ice cube in a plastic bag of water on her dorsal forearm for 5 minutes, then assessing the area ten minutes after removal. No skin changes were appreciated at the site of the ice cube, but she did develop urticaria over both patellae. Diphenhydramine was provided, with resolution of pruritus and urticaria. The remainder of her physical exam was unremarkable.

Based on the suggestive symptoms and CST, the patient was diagnosed with idiopathic cold urticaria. She was informed that this disease is likely to resolve in a matter of years and was instructed to take cetirizine 10 mg daily as prophylaxis, in addition to diphenhydramine for flares. She was also advised to avoid immersion in cold water and provided with a prescription for epinephrine auto-injectors should she develop systemic symptoms.

Discussion

Cold urticaria is a unique disorder that may be diagnosed with a thorough history and a noninvasive CST. Using an ice cube in a plastic bag of water, this test is both sensitive and specific for cold urticarial (83-90% and 100%, respectively^{5,6}). With the development of urticaria at a site distant to ice cube placement, this particular patient's response to the CST was unexpected. Interestingly, Kim et al (2006) described a similar case in which a 15-year-old female developed urticaria on her bilateral knees and elbows following CST,⁷ but we were otherwise unable to find reports of or explanations for this phenomenon. We do not believe this patient's development of patellar

urticaria was a random eruption unrelated to the CST, as her arms and legs had been exposed for more than thirty minutes prior to this. It is possible that the knees and elbows, both extensors, are predisposed to a lower threshold for cold urticaria, but explanations of a mechanism are lacking.

Even as her CST was technically negative because she did not develop a wheal at the site of ice cube contact, we believed the eruption of hives at a distant site still suggested cold urticaria. We also favored her disease to be idiopathic, as her history did not suggest a postinfectious etiology. Among other organisms, cold urticaria has been linked to *Helicobacter pylori*⁸ and infectious mononucleosis,⁹ neither of which were suggested by her history. Cold urticaria has also been observed to be genetic in diseases like familial atypical cold urticaria and familial cold autoinflammatory syndrome. Both of this patient's parents were adopted, and we were thus unable to fully evaluate a family history. However, these diseases were exceedingly unlikely given her age of onset and lack of systemic symptoms.

As cold urticaria is the result of histamine release from mast cells, the staples of treatment are medications to block histamine's effects. First or second generation H1 antihistamines accomplish this goal, although second generation antihistamines such as cetirizine are preferred for daily prophylaxis given their lack of anticholinergic side effects. Ultimately, a trial of different antihistamines and doses may be required to find an acceptable balance between efficacy and side-effect tolerance. Moreover, a higher dose than usual is often required to control symptoms, as illustrated by Siebenhaar et al in 2009¹⁰ and subsequent studies.^{11,12} In addition to prophylactic medication, an additional antihistamine, such as diphenhydramine, may be used for breakthrough urticaria. While the majority of patients may be adequately controlled with this regimen, other medications, such as leukotriene antagonists, H2 antihistamines, antibiotics, and corticosteroids, may be added for additional preventative

symptom control. In addition, more innovative medications with more severe side-effect profiles may be options for refractory disease. For instance, the anti-IgE antibody omalizumab has been used successfully,¹³ as has cyclosporine¹⁴ and etanercept.¹⁵

While the pruritus and visual rash may be frustrating and aggravating, there may be life-threatening consequences of missing a diagnosis of cold urticaria. The effects of mast cell degranulation are not always limited to the skin, and systemic anaphylactic reactions are possible, especially following immersion in cold water. This patient was prudent to avoid swimming in the frigid waters of Lake Michigan, as the consequences of this could have been fatal. Counseling to avoid situations that place patients at risk of this is crucial, as is providing them with the means to be treated quickly with an epinephrine auto-injector, especially if they have a history of anaphylaxis, systemic symptoms, frequent and unavoidable cold exposure, and/or a high temperature threshold.

Due to the possibility of anaphylaxis, it is important not to miss the diagnosis of cold urticaria. Although a suggestive history and CST are often sufficient for making a diagnosis, this patient's development of urticaria at a remote site after CST suggests that clinicians who suspect this disease should remain vigilant even if urticaria does not develop at the site of ice cube placement. Instead, it is reasonable to recommend that in this situation, the clinician should ask the patient if he or she has developed new areas of pruritus and inspect the patient's knees and elbows.

Conclusion

Cold urticaria may be diagnosed with a suggestive history and positive CST. This test provides the stimulus for mast cell degranulation, but the phenomenon of this occurring at a site remote to where the stimulus was placed is not well described in the literature, and to our knowledge, a mechanism has not previously been studied. As anaphylaxis is a potential consequence of missing

this diagnosis, we suggest taking additional measures when a patient has a suggestive history but negative CST. These measures, which include asking the patient if he or she has developed new areas of pruritus since ice cube placement and inspecting the patient's knees and elbows, may increase the sensitivity of the test.

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