

Diagnosis and Management of Cold Urticaria

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PRACTICE POINTS

- Cold urticaria is a physical urticaria characterized by a localized or systemic eruption of papules upon exposure of the skin to cold air, liquids, and/or objects.
- Symptoms of cold urticaria, which range from erythema, pruritus, and hives to angioedema and sometimes anaphylaxis, may be debilitating for patients; therefore, effective treatment is required to improve quality of life.
- First-line treatment for cold urticaria includes second-generation H₁ antihistamines at up to 4 times the standard dosage.

Cold urticaria is a physical urticaria characterized by a localized or systemic eruption of papules upon exposure of the skin to cold air, liquids, and/or objects. In some cases, angioedema and anaphylaxis also may occur. The symptoms of cold urticaria can have a negative impact on patients' quality of life. Second-generation H₁ antihistamines are the first line of treatment in cold urticaria; however, patients who are unresponsive to initial treatment with H₁ antihistamines may require further management options. Avoidance of cold exposure is the most effective prophylactic measure. In mild to moderate cases, the primary goal of therapy is to improve the patient's quality of life. In more severe cases, treatment measures to protect the patient's airway, breathing, and circulation may be necessary. We report the case of a 23-year-old man with cold urticaria who was refractory to initial therapy with H₁ antihistamines. A review of the literature also is provided.

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Cold urticaria is a rare condition characterized by a localized or systemic eruption of papules upon exposure of the skin to cold air, liquids, and/or objects. In some cases, angioedema and anaphylaxis can occur. The wheal-and-flare reaction results from a localized or systemic release of histamine, leukotrienes, and various other proinflammatory mast cell mediators. Cold urticaria can be acquired or follow an autosomal-dominant familial transmission pattern. Acquired cold urticaria often presents in young adulthood with a mean duration of 4 to 5 years and remission or improvement of symptoms after 5 years in 50% of cases.¹ The familial variant most commonly presents in early childhood and endures throughout the patient's life.² Cold urticaria generally is classified as acute or chronic if symptoms persist for more than 6 weeks. Pharmacologic therapies with prophylactic effects that may reduce the intensity of symptoms or inhibit their development include antihistamines, leukotriene receptor antagonists, biologics, and glucocorticoids. We present the case of a 23-year-old man with cold urticaria that was refractory to initial treatment with H₁ antihistamines along with a review of the literature.

Case Report

A 23-year-old man presented to the dermatology clinic for evaluation of recurrent burning, itching, and sometimes development of a painful rash on the

face, neck, and arms of 2 years' duration that typically occurred following exposure to cold, wind, and rain. He also developed symptoms in warm weather when exposed to wind while sweating. His medical history was remarkable for asthma, which was not active. He was not taking any medications and had no known drug or environmental allergies. No other members of his household developed similar symptoms. His only successful means of prevention was to stay indoors, which thereby limited his activities.

Physical examination of the dorsal hands following an ice cube test revealed numerous 3- to 5-mm urticarial papules with surrounding erythema (Figure).

Following the initial evaluation, the patient was treated unsuccessfully with a mix of first- and second-generation antihistamines in gradually increasing doses to a maximum dose of loratadine 20 mg once daily, cetirizine 20 mg once daily, and hydroxyzine 20 mg once daily. A course of montelukast 10 mg once daily was started in addition to the antihistamines and led to a reduction in the severity of the lesions but not the frequency and did not relieve the burning sensation; the patient subsequently discontinued therapy. Next, a trial of cyclosporine was attempted, but the patient reported that it caused emesis and subsequently discontinued treatment. The patient also did not tolerate prednisone. He eventually decided to treat his symptoms with lifestyle choices only, such as making sure to be well covered in cold temperatures.

Comment

Cold urticaria is a physical urticaria resulting from mast cell degranulation and the subsequent release of histamine and proinflammatory cytokines upon exposure of the skin to cold air, liquid, and/or objects. Symptoms usually are limited to localized exposed areas of the skin but also can be generalized. Cold urticaria typically manifests as erythematous, pruritic papules and also may be accompanied by deep tissue involvement resulting in angioedema and/or anaphylaxis. Symptoms usually occur within minutes of cold exposure; however, in delayed-type cold urticaria, symptoms may develop 24 to 72 hours later.³ Prevalence is relatively equal in both sexes and is highest among young adults (ie, 18–27 years old), with a greater incidence associated with cold climates.⁴ In one study, the overall incidence of acquired cold urticaria in Central Europe was estimated to be 0.05%.¹

Systemic involvement may occur with extensive cold contact, ranging in severity from generalized urticaria to anaphylaxis and involvement of the cardiovascular, respiratory, and/or gastrointestinal systems.⁵ Patients who exhibit systemic responses to cold exposure should avoid swimming in cold water, as this may induce anaphylaxis and result in injury or



Urticarial papules on the right hand following an ice cube test.

death. In a 2004 study that included 30 children with cold urticaria at a tertiary center in Boston,⁶ 11 (36.7%) participants who underwent cold stimulation testing developed systemic symptoms; 5 (45.5%) participants experienced respiratory distress and 8 (72.7%) experienced a decrease in level of consciousness (eg, faintness, dizziness, hypotension). Aquatic activity was the trigger in all 11 participants except for 1 (9.0%), who experienced systemic symptoms on exposure to cold air. In the same study, 14 (46.7%) participants were diagnosed with asthma and 15 (50%) were diagnosed with allergic rhinitis. Of the 28 participants whose family histories were available for review, 25 (89.3%) had a family history of atopic disease.⁶ A 2008 Greek study⁴ of 62 adults with acquired cold urticaria found that 18 (29%) participants had at least 1 serious systemic response resulting in generalized urticaria or angioedema associated with hypotension (eg, dizziness, fainting, disorientation, shock). In both of these studies, a majority of the serious systemic reactions were associated with cold water activities.

Cold urticaria is primarily an idiopathic phenomenon but can be classified as acquired or familial. Acquired cold urticaria may result from primary or secondary causes, which can include cryoglobulinemia, human immunodeficiency virus, syphilis, mononucleosis, rubeola, toxoplasmosis, varicella, hepatitis, and various drugs (eg, penicillin, angiotensin-converting enzyme inhibitors, oral contraceptives).⁷ Familial causes include cryopyrin-associated periodic syndrome, phospholipase C2 gene-associated antibody deficiency and immune dysregulation, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.

Typically, cold urticaria is diagnosed using cold stimulation tests such as the ice cube test, in which

an ice cube is applied directly to the patient's skin for 3 to 5 minutes and a response is measured 10 minutes after its removal.⁸ This test has been shown to have a sensitivity of 83% to 90% and a specificity of 100%.⁹ Alternatively, cold urticaria may be diagnosed through the use of a Peltier element-based cold-provocation device, which exposes the patient to a variety of temperatures in order for clinicians to determine the threshold upon which there is an observable reaction. With a sensitivity of 93% and specificity of 100%, the accuracy of this test is similar to that of the ice cube test.¹⁰ If a patient has a history of serious systemic involvement, any testing that exposes the patient to extensive cold exposure should be used with caution.

Patients should be counseled about potential serious systemic symptoms and the importance of wearing appropriate cold-weather clothing. Avoidance of cold water activities and overexposure to cold weather also should be emphasized. Pharmacologic therapy for prophylaxis typically includes a second-generation H₁ antihistamine (eg, cetirizine, loratadine, desloratadine). Since these drugs have been shown to be less sedating than first-generation antihistamines, they are considered a better choice for chronic treatment. At high doses, however, these medications may have a sedative effect; therefore, nighttime use is preferable if possible. The standard dosage is 5 mg to 10 mg daily for oral cetirizine, 10 mg daily for oral loratadine, and 5 mg daily for oral desloratadine; however, up to 4 times the standard dosage of these medications may be required for effective treatment of cold urticaria.¹¹ Given the associated risk of anaphylaxis, patients should be prescribed an epinephrine pen and educated about its appropriate use, including the importance of keeping the pen accessible at all times.

In refractory cases of cold urticaria, an H₂ antihistamine (eg, ranitidine) can be used in conjunction with H₁ antihistamines.¹² Omalizumab, an IgE-mediated treatment, also has been shown to be safe and effective in patients with recalcitrant physical urticaria, including cold urticaria.^{13,14} One report described the case of a 69-year-old woman with cold urticaria who was unable to leave the house without developing a widespread eruption on the face, trunk, and limbs.¹⁵ After undergoing a series of unsuccessful treatments, the patient was started on cyclosporine 125 mg twice daily, which was reduced to 100 mg twice daily after 4 weeks of therapy and then reduced to 75 mg twice daily after 4 months of treatment. One week after therapy was initiated the patient reported that she was able to leave the house, and after 4 weeks of treatment the lesions only developed on the hands and feet. The patient remained in remission with a low-dose therapy of cyclosporine 75 mg twice daily with lesions only occurring on the hands and feet.

The low-dose maintenance therapy was associated with minimal adverse effects.¹⁵ To our knowledge, there are no known large studies on the efficacy of cyclosporine in the treatment of cold urticaria.

Leukotriene receptor antagonists (eg, montelukast, zafirlukast, zileuton) have been used to treat chronic urticaria. In one report, montelukast was used in a 29-year-old woman with cold urticaria who had initially been treated with cetirizine 30 mg daily, cyproheptadine 4 mg daily, and doxycycline 200 mg daily with minimal to no relief. After treatment with montelukast, she experienced notable and stable improvements in symptoms.¹⁶ Hydroxychloroquine also has been shown to be safe and to substantially improve quality of life in patients with idiopathic chronic urticaria.¹⁷ Methotrexate (with close patient monitoring for adverse effects) has been reported to benefit some patients whose chronic urticaria was unresponsive to standard treatment.¹⁸ Treatment regimens for chronic urticaria have shown variable success in the treatment of cold urticaria and may be considered in cases refractory to treatment with high-dose second-generation H₁ antihistamines.

Topical application of capsaicin for 4 to 7 days has been shown to deplete the neuropeptides in sensory fibers that may be involved in cold reactions, although skin irritation may prevent usage.¹⁹

Prednisone therapy was used in a small study of 6 patients with acquired cold urticaria.²⁰ Three patients were treated for periods of 3 to 5 days with prednisone 20 mg each morning. Three other patients were given a single dose of prednisone 20 mg or 25 mg in the morning, depending on body weight. Following prednisone therapy, complete or partial pruritus was subjectively improved in all 6 patients. Additionally, significant reductions in venous histamine concentrations at 5 and 10 minutes following cold immersion were noted ($P < .05$ and $P < .025$, respectively); however, no significant improvement in either erythema or edema was noted posttreatment following cold immersion.²⁰ Despite these findings, prednisone has not been shown to consistently prevent histamine release. Another report noted the case of a 47-year-old man with cold urticaria who required hypothermic cardiopulmonary bypass. Pretreatment with prednisone 20 mg daily and preoperative hydrocortisone 100 mg intravenously did not prevent histamine release.²¹

Cold desensitization (ie, exposing progressively larger areas of the patient's skin to increasingly colder water) may induce tolerance to cold and decrease the temperature threshold at which symptoms develop; however, patients with known serious systemic reactions should be tested with extreme caution and only under the supervision of a clinician.^{22,23} Tolerance may wane when cold desensitization therapy is stopped.

The prognosis for patients with acquired cold urticaria generally is good. Improvement of symptoms or full remission occurs within 5 to 6 years in 50% of patients.²⁴ Once remission has occurred, patients generally remain symptom free. For other familial variants, symptoms may last a lifetime.

Conclusion

This case report and review of the literature highlights the limitations of cold urticaria and the importance of effective management in improving quality of life in affected patients. Symptoms may limit patients' ability to work in certain environments, inhibit them from engaging in daily activities, and even prevent them from leaving their homes in colder temperatures. In addition to behavioral modifications, pharmacologic management may provide symptomatic relief. Antihistamines are the first line of treatment in cold urticaria. Second-generation antihistamines, which are more selective for H₁ receptors and less sedating, are generally recommended. Up to 4 times the standard dosage of these medications may be required for effective treatment.⁵ The primary goal of therapy in mild to moderate cases is improvement in quality of life.

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