

# Pearls and pitfalls: Cold-induced urticaria

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### ABSTRACT

**Background:** Cold-induced urticaria can take place either due to direct cold exposure, cryoglobulinemia, or genetic component (such as cryopyrin-associated periodic syndrome), which leads to the rapid onset of urticaria and/or angioedema. It is more common in younger patients and more likely to affect females compared with males.

**Objective:** To increase awareness of such systemic reactions of anaphylaxis and provide a focused review of the differential diagnosis, underlying mechanisms, broad workup, and management of this disease process for allergy/immunology fellows, residents, general physicians, and general practitioners.

**Methods:** Pertinent information was included from the patient's clinical course. Also, a review of the available literature to include additional references that were obtained by using the works cited in the most up-to-date reviews was completed.

**Results:** A case of a patient with cold-induced urticaria with common sequela was presented, followed by a discussion of the pathophysiology, diagnosis and its differential diagnosis, workup, and management.

**Conclusion:** Cold-induced urticaria is a complex disease with several different catalysts. Providers should be aware of the different forms of cold-induced urticaria and recognize the risk for anaphylaxis in this patient population. Pearls and pitfalls of the diagnosis and management are provided.

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### QUESTION

A 23-year-old woman with a history of asthma and allergic rhinitis presents to her physician's office with history of urticaria present on an intermittent basis over the past 6 months. There is no history of similar urticarial episodes. The patient reports that symptoms only arise when in cold environments, such as the freezer section of the supermarket, or with direct contact, such as holding a cold drink. Although swimming in the ocean does lead to scattered urticaria, no angioedema and no systemic symptoms have been reported. The patient does not have arthralgias, fevers, or a personal or

family history of hearing loss. There are no family members with similar symptoms. The patient has not tried pretreating or routinely taking antihistamines, and diphenhydramine use is limited to as needed after the onset of symptoms, which has been of benefit. Human immunodeficiency virus (HIV) and cold agglutinin testing both return negative results. What would be the best initial management plan for this patient?

### POSSIBLE ANSWERS

- A. Avoidance of all cold stimuli.
- B. Start omalizumab therapy in this patient
- C. Prescribe nonsedating antihistamine medication up to four times the standard dosing based on dose-dependent symptom resolution.
- D. Prescribe an epinephrine autoinjector.
- E. Both answers A and D.

### INTRODUCTION

Cold-induced urticaria (CU) is an uncommon physical urticaria that can present with mild to severe symptoms within minutes of exposure. In a recent 2016 retrospective study, Deza *et al.*<sup>1</sup> found that almost 20% of their patients with CU presented with life-threatening reactions to cold. The result after cold exposure is a release of histamines and pro-inflammatory mast cell mediators that causes pruritic wheals with or without angioedema. This can be a mild localized reaction that

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**Table 1 A list of possible laboratory testing to order in the investigation of cold-induced urticaria\***

|                                                                |
|----------------------------------------------------------------|
| Circulating cryoglobulins                                      |
| Cold agglutinins                                               |
| Serum C4                                                       |
| Erythrocyte sedimentation rate                                 |
| C-reactive protein                                             |
| Complete blood cell count with differential                    |
| Serum amyloid A                                                |
| Genetic testing ( <i>NLRP3</i> [ <i>CIAS1</i> ] gene mutation) |
| Skin biopsy                                                    |

*\*This is an extensive list, and providers should select laboratory tests based on the history and clinical picture of the individual patient.*

resolves with avoidance of continued cold stimuli, or it can be more severe, with systemic manifestations. CU can be classified into primary and secondary acquired CU. Primary acquired CU, the more common presentation, is urticaria produced by a cold stimuli without a secondary trigger etiology. Secondary acquired CU is urticaria that manifests after a cold stimulus that follows an initial triggering etiology, such as infection or medications. For most patients with primary acquired CU, the duration of symptoms lasts for 4.8–7.9 years, with remission or improvement of symptoms after 5 years in half of the cases.<sup>2</sup> Besides the typical CU presentation, providers should be aware of other components of the differential diagnosis, including cryoglobulinemia and cryopyrin-associated periodic syndrome (CAPS).

## CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

Patients, mostly of the female gender, commonly present with CU at a young adult age and with a history of asthma (46.7%), allergic rhinitis (50%), and/or a family history of atopic disease (89.3%).<sup>1</sup> Pertinent to the diagnosis of CU is a thorough history and physical examination of patients who exhibit symptoms with cold stimuli. Common triggers are skin exposure to cold air (especially seen in northern countries), cold liquid, or other cold objects. More systemic contact or a broader area of exposure increases the chances of a systemic or anaphylactic reaction.

For primary acquired CU, mast cells are activated by cold stimuli, which causes a localized or systemic release of histamines and pro-inflammatory mediators, and leads to a pruritic wheal-and-flare reaction. From a thorough study by Meyer *et al.*,<sup>3</sup> in 2013, mast cell degranulation is suggested to be the main feature that differentiates the consequences of cold exposure between individuals without CU and those with CU. Once mast cells are stimulated, they release a

significant amount of histamine, which increases blood flow, thermal warming, vasodilation, and recruitment of collateral circulation.<sup>3</sup> It is the histamine and not leukotriene C4 that plays a role in mediating the CU pruritic wheals.<sup>4</sup> Although there is a local release of tryptase, it seems that this does not have a role in the pathophysiology of CU.<sup>3</sup> It also seems that mast cells and not basophils or other white blood cell types are responsible for the urticaria reaction in CU.<sup>3</sup>

The most common cause of secondary acquired CU is cryoglobulinemia. Cryoglobulinemia is a rare disorder defined as the presence of cryoglobulins in the blood. With cold temperatures, infections (*e.g.*, infectious mononucleosis, respiratory viral infections, hepatitis)<sup>5</sup> or immune-mediated disorders (*e.g.*, HIV, chronic lymphocytic leukemia, lymphosarcoma)<sup>6</sup> cause mixed polyclonal cryoglobulin proteins with immunoglobulin E (IgE) disproportionately higher that can clump together, restricting blood flow to joints, muscles, and organs. A proposed mechanism behind secondary acquired CU urticaria is the inverse relationship between high IgE and CD4 depletion. In HIV particularly, there is evidence for loss of T-helper (Th) type 1 cells, increasing Th2 cells, with subsequent release of interleukin (IL) 4, upregulating IgE synthesis. This increased amount of circulating IgE is directed against the skin or mucosal antigen when exposed to low temperatures, which results in mast cell degranulation and CU.<sup>6</sup>

Also, there are heritable forms of CU, termed CAPS. CAPS is a rare inherited group of autoimmune disorders that lead to IL-1 $\beta$  overproduction. Mutations in the gene *NLR Family Pyrin Domain Containing 3* (*NLRP3*) alter the cryopyrin protein, which, in activating caspase-1 and IL-1 $\beta$ , leads to mast cell degranulation and urticaria. The three disorders that constitute CAPS are the following: familial cold autoinflammatory (or urticaria) syndrome (FCAS/FCU), Muckle-Well syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurologic cutaneous articular syndrome). These three disorders represent a continuum of disease severity, with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome representing the most severe form, Muckle-Well syndrome representing an intermediate form, and FCAS/FCU representing the milder end of the disease process. These disorders are missense mutations in the cryopyrin gene inherited in an autosomal dominant fashion. Most patients with CAPS will present early in life with fever and delayed urticarial and/or angioedema response to cold stimuli.<sup>7</sup>

## DIAGNOSIS

To diagnosis CU, acquiring a history is paramount. Providers should discuss how the urticaria develop on

**Table 2 Management of cold-induced urticaria**

|                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Avoidance                                                                                                                                                                                           |
| Counseling                                                                                                                                                                                          |
| Swim with a buddy                                                                                                                                                                                   |
| Bundle up appropriately in cold weather                                                                                                                                                             |
| Nonsedating second-generation H <sub>1</sub> antihistamine (such as cetirizine, loratadine, or desloratadine) up to four times the standard dosage                                                  |
| Add H <sub>2</sub> antihistamine to H <sub>1</sub> antihistamine for synergistic effects                                                                                                            |
| Omalizumab dosing <i>via</i> body weight and total immunoglobulin E levels per U.S. Food and Drug Administration approved recommendations                                                           |
| Desensitization                                                                                                                                                                                     |
| Epinephrine autoinjector for patients at high risk (those with urticaria to cold water immersion, those with oropharyngeal reactions, and those with a history of systemic symptoms or anaphylaxis) |

exposure to cold stimuli and if cold water immersion was present. The history should elicit information with regard to the rash's appearance and associated symptoms (fevers, joint pain, emesis, diarrhea, abdominal pain) as well as uncovering other inciting events besides cold stimuli.

To support a suggestive history, cold provocation testing can be performed. The traditional protocol consists of applying a melting ice cube in a thin plastic bag to the patient's volar forearm for 5 minutes. A positive test result is defined as a wheal formation within 10 minutes after the ice cube stimulus is removed. This test has been shown to have a sensitivity of 83% and a specificity of 100%. If determining cold temperature thresholds, then low-voltage Peltier thermoelectric elements (TempTest method) can be used. The sensitivity is 93%, and the specificity is 100%. The TempTest method is helpful in assessing critical temperature thresholds because thresholds are useful markers for CU severity.<sup>8</sup> Laboratory tests that should be considered to probe the differential diagnoses of CU, guided by clinical picture and judgment, are the following: serum cryoglobulins and/or cold agglutinins (if concern for secondary acquired CU), C-reactive protein, erythrocyte sedimentation rate, amyloid A (if concerned for FCAS), and genetic testing if concerned for CAPS (Table 1).

## MANAGEMENT

Patients with CU have severely impaired daily lives, especially for those with high temperature thresholds and who live in colder regions of the world. The mainstay of management is avoidance. Patients should avoid cold stimuli, whether it is cold foods, cold liquids, cold air, or swimming in a cold body of water. If the stimuli is cold air, then patients should be instructed to bundle

clothes appropriately to maintain a warmer body temperature. For those who have anaphylactic reactions, it is important to participate in some activities, *e.g.*, swimming in a cold water, with a buddy and to maintain ready access to an epinephrine autoinjector (Table 2).

If symptoms are worse or avoidance is not possible, then a nonsedating second-generation H<sub>1</sub> antihistamine (such as cetirizine, loratadine, or desloratadine) up to four times the standard dosage can be given.<sup>9</sup> For refractory cases, H<sub>2</sub> antihistamine (*e.g.*, ranitidine) can be combined with H<sub>1</sub> antihistamine for a synergistic effect.<sup>10</sup> Another promising pharmacologic intervention for CU, which is now U.S. Food and Drug Administration approved for CU, is omalizumab, an anti-IgE-mediated medication.<sup>9</sup> In some anecdotal studies, the use of a leukotriene antagonist (*e.g.*, montelukast) has been suggested as effective at reducing urticaria. Yet, in a more recent trial, a leukotriene antagonist was not effective and Leukotriene C<sub>4</sub> (LTC<sub>4</sub>) was not shown to be released in the CU wheal.<sup>4</sup> If a patient sustains a systemic reaction, then the life-saving mainstay of therapy is epinephrine, which should be administered as soon as possible (Table 2).

To conclude, CU can have multiple stimuli that, when not avoided or when suitable interventions are not applied, can lead to life-threatening outcomes and even death. It is important for clinicians to recognize CU, understand the underlying pathophysiology, and provide appropriate management.

## CORRECT ANSWER TO POSED QUESTION

- Incorrect. The patient in this case scenario has primary CU, and thus the mainstay in management is avoidance of cold stimuli. However, this patient also has CU induced by cold water immersion, an indication for maintaining an epinephrine autoinjector.
- Incorrect. The question specifically asks what is the initial management for this patient. If this patient cannot avoid cold stimuli or if symptoms worsen with attempted avoidance, then the next step in management is nonsedating H<sub>1</sub> antihistamine. When drawing from the well-established literature, doses of up to four times the standard daily dosage can be titrated to symptom response.
- Incorrect. Again, this is secondary management after avoidance and nonsedating H<sub>1</sub> antihistamine. Although omalizumab is U.S. Food and Drug Administration approved for CU management, it is not a primary management modality in most cases of CU.
- Incorrect. This is correct; however, this is not the best answer choice given. An epinephrine autoinjector should always be given to patients whose urticaria is induced by cold water immersion, who have experienced oropharyngeal reactions associated with cold

stimuli, and those patients with a history of systemic symptoms or anaphylaxis.

- E. Correct. Because this patient exhibits signs and symptoms of primary CU, which is also induced by cold water immersion, the best initial management is to avoid cold stimuli and to prescribe an epinephrine autoinjector.

## PEARLS

- A thorough, detailed history is the most important tool to help determine if your patient has CU and whether it is primary or secondary acquired CU. Additional testing and diagnostic modalities should be guided by the patient's history.
- If results of an examination are positive for urticaria and arthralgia, then CAPS should be suspected and genetic testing that looks at *NLRP3* should be performed.
- Due to the serious potential of anaphylaxis associated with CU, patients should be counseled on this and be provided an epinephrine autoinjector to patients with urticaria induced by cold water immersion and oropharyngeal reactions associated with cold stimuli, and those patients with a history of systemic symptoms or anaphylaxis.

## PITFALLS

- CU is a complex disease with several catalysts, thus it is also important to consider other elements of the differential diagnosis, such as CAPS.

- Providers should remain aware that ~20% of patients with CU have a negative ice-cube challenge.<sup>8</sup>

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