



A “Stadium” Urticaria, Cold Urticaria Is Still a Mostly Unknown Disease, with a Wide Spectrum of Severity Degrees and Few Therapeutic Certainties: Is Omalizumab One of These? Reflections from a Clinical Case Report

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Abstract

Introduction: One of the most common forms of physical urticaria is the cold urticaria. It can be a medical emergency, since it can induce anaphylaxis and edema of the glottis, and in any case, it is a condition that reduces the quality of life of the affected subjects forced to significantly limit their normal activities. Moreover, since the symptoms are triggered by exposure to cold, which is difficult (if not impossible) to avoid in everyday life, a safe and effective therapy appears to be essential. Unfortunately, traditional therapies often cannot provide adequate and safe answers.

Case Presentation: The current study reported the case of a 52-year-old female patient manifesting the first symptoms after going to the stadium to watch football games while sitting in the stands. On such occasions, her buttocks would begin to itch, and started swelling and reddening. These manifestations then occurred on other occasions of exposure to the cold, and in other body areas. The patient visited the outpatient clinic of Allergy and Clinical Immunology Unit, Teramo General Hospital (Teramo, Italy), and was treated with sedating and non-sedating H1-blocking antihistamines (Rupatadine, Cetirizine), a leukotriene antagonist, and oral steroids with no success; therefore, it was decided to treat her with Omalizumab, an anti-IgE antibody.

Conclusions: The satisfactory response to Omalizumab in the patient, after the failure of previous standard therapeutic strategies, confirmed the effectiveness of this molecule to treat cold urticaria, which despite what reported in several studies, is not yet recognized and authorized by the competent health authorities in the treatment of this condition.

Keywords: Allergy, Anaphylaxis, Antihistamines, Anti-IgE Antibody, Cold, Immunology, Leukotriene Antagonist, Omalizumab, Oral Steroids, Physical Urticaria, Urticaria

1. Introduction

Cold urticaria (CU) is one of the most common forms of physical urticaria, accounting for one-third of all cases (1). It is a serious form of chronic inducible urticaria, with higher rates of incidence in colder climates and females, and with the most common onset observed in young adults.

Symptoms are triggered by exposure to objects, water, and air at temperatures lower than the body.

Wheals and/or angioedema manifest within minutes and persist for up to two hours after the contact with the cold site/object.

Up to one-third of people could experience systemic symptoms such as fatigue, headache, or generalized ur-

ticaria, up to anaphylaxis. Swimming in cold water- or the full immersion of the body in cold water/an extensive contact with cold-could induce dangerous systemic reactions/anaphylaxis.

Similar risks could be the consequence of surgical procedures or the infusion of cold intravenous solutions.

Despite the severity of the possible clinical pictures, cold urticaria is still understudied, and the authors' knowledge about the condition, its natural history, and the factors that determine the prognosis and help to make therapeutic decisions is limited.

From the clinical point of view, cold urticaria is classified into three types, in two possible classification attempts, as shown in Tables 1 and 2 (2, 3).

The condition through sensory nerve activation, va-

Table 1. Clinical Classification of Cold Urticaria

Cold Urticaria Classification	Type I	Type II	Type III
Symptom	Localized urticaria and/or angioedema	Generalized urticaria and/or angioedema without hypotensive or respiratory symptoms	Severe systemic reactions with ≥ 1 episode suggesting respiratory distress (wheezing or shortness of breath) or hypotension (dizziness, sensation of fainting, disorientation, or shock)
Management	Protection from extreme cold and antihistamines	Protection from extreme cold and antihistamines	Prescribe an epinephrine auto-injector

Table 2. Pathogenetic Classification of Cold Urticaria

	CST	Details
Primary acquired cold urticaria	Immediate positive	Familial forms are rare, and characterized by earlier onset and involvement of other systems It develops secondary to a systemic infectious or autoimmune disease
Secondary cold urticaria	Immediate positive	Causes include: Cryoglobulinemia with or without malignancies, infections (HIV, hepatitis, syphilis, parasites, bacterial infections) Similar manifestations: Leucocytoclastic vasculitis and cold agglutinin disease
Atypical cold urticaria	Negative	Manifestations similar to those of other types of cold urticaria; however, it usually involves more severe reactions, including symptoms such as hypotension Sub-classified into several forms- including systemic, localized, cold-induced cholinergic urticaria, cold dependent dermatographism, delayed cold urticaria and localized cold-reflex urticaria

sodilatation, plasma extravasation, and cell recruitment is due to mast cell degranulation, and the subsequent release of platelet-activating factor (PAF), pro-inflammatory cytokines, and histamine. Mast cell-activating signals are heterogeneous and diverse, probably specific to each type of urticaria.

Although the precise pathogenetic mechanism underlying cold urticaria is still mostly unknown, IgE seems to play a relevant role, at least in some cases.

Few studies and some case reports are available, reporting the effectiveness of treatments in cold urticaria as a specific entity.

Considering the possible severity of symptoms and the difficulty-if not impossibility-of avoiding cold in everyday life, it is easy to understand the need for an effective cure.

The treatment of cold urticaria aimed at the complete control of the symptoms and the triggering of the disease still involves a step-by-step approach.

In many patients, antihistamine therapy is inadequate to control the development of symptoms of cold urticaria, even with higher than the standard doses.

More specifically, second-generation antihistamines were better than placebo to treat Cold urticaria; besides, up-dosing to four times the standard dosage may be effective.

On the other hand, other treatments such as Cyproheptadine and Doxepin did not provide the same evidence (4).

In the literature, cases treated with con Anakinra (human interleukin (IL)-1 receptor antagonist (r-metHuIL-1ra)

(5), Etanercept (human tumor necrosis factor receptor (p75) Fc fusion protein) (6), and Reslizumab (humanized monoclonal anti-IL-5) were also described (7).

The current management of the disease is often unsatisfactory, and unable to induce the resolution of the symptoms, or at least a significant clinical improvement with the achievement of adequate patient safety; it is, therefore, necessary to find a new effective and safe therapeutic strategy.

Currently, Omalizumab- a recombinant humanized immunoglobulin (Ig) G1 monoclonal antibody- is approved to treat chronic urticaria and asthma, and is now used off-label in several conditions to evaluate its effectiveness and safety in the management of other conditions (8).

Omalizumab binds to IgE and prevents the binding of the latter to FcεRI (high-affinity IgE receptor), thereby reducing the amount of free IgE that is available to trigger the allergic cascade, preventing their binding to the specific receptor on mast cells and other effector cells. The treatment of atopic subjects with Omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils (9).

Omalizumab is effective in many cases of cold urticaria (Table 3) (1, 8, 10).

The current study patient provided written informed consent for the publication of this report and any associated images.

2. Case Presentation

The current study reported the case of a 52-year-old female patient with cold urticaria for one year treated with sedating and non-sedating H₁-blocking antihistamines (Rupatadine, Cetirizine), a leukotriene antagonist, and oral steroids, without success.

The patient, a football fan, began to complain of the first disorders over a year ago; she could not understand why, shortly after arriving at the stadium to watch a game, her buttocks would begin to feel itchy, while reddening and swelling. Upon returning home, her symptoms quickly regressed. Afterward, the same disorders began to affect her hands, after taking cold objects, her arms, while resting on a marble sill, and her face, after the exposure to cold winter air. Urticaria only affected the body areas in contact with the cold. The patient visited the outpatient clinic of Allergy and Clinical Immunology Unit, Teramo General Hospital, Teramo, Italy, on February 2016, to complain about these disorders that appeared suddenly and mysteriously, and regressed in a variable and equally mysterious way. The condition-despite her passion for football-made her desist from going to the stadium to watch the game of her team. However, she still could not make a direct connection with the exposure to cold.

She had no significant co-morbidities and did not take any drugs, no atopic family members, and nobody with similar disorders.

The assessment of her cold urticaria showed an uncontrolled disease before the treatment with urticaria control test (UTC) (Table 3).

The patient was advised not to expose herself to strong temperature variations, stay in cold environments for a long time, bath in cold water, and have contact with cold objects or food.

The Cold Urticaria diagnosis was based on the criteria of the EAACI/GA2LEN/EDF/WAO guidelines (2017 revision and update) to define, classify, diagnose, and manage urticaria (11).

The ice cube provocation test revealed positive results within less than five minutes (Figure 1), with the development of itch, wheals, and redness.

Autologous serum skin test, erythrocyte sedimentation rate, complete blood count, standard biochemical profile, serum protein electrophoresis, C-reactive protein, total IgE levels, anti-neutrophil antibody, rheumatoid factor, complement 3 and 4, C1 esterase inhibitor, anti-double-stranded DNA, anti-extractable nuclear antigens, anti-thyroglobulin/anti-thyroid peroxidase antibodies, most common viral, bacterial, and parasite infections, cryoglobulins, and research for factor XII mutations were all within the normal ranges (12).

After receiving the patient's informed consent, in compliance with the rules of the institution, Omalizumab was administered off-label (300 mg via subcutaneous injection per month, for six months) at room temperature. The dose of Omalizumab administered to the patient was the same recommended in the treatment of chronic spontaneous urticaria. Rupatadine was gradually reduced and discontinued in the second month of Omalizumab therapy.

No side effects were observed at the injection site.

The patient reported a significant improvement after the second injection, and she was free of symptoms three months later. She started going to the stadium once again. Repeated ice cube provocation test produced negative findings. At a six-month follow-up, symptoms remained controlled without any further treatment. The assessment of the cold urticaria is reported in Table 4.

Table 4. Urticaria Control Test Scores of the Patient Evaluated Monthly Before, During, and After the Treatment with Omalizumab

Treatment	Test Scores
Before treatment	6
One month after first omalizumab injection	8
One month after second omalizumab injection	11
One month after third omalizumab injection	16
One month after fourth omalizumab injection	16
One month after fifth omalizumab injection	16
One month after sixth omalizumab injection	16
Two months after last omalizumab injection	16
Three months after last omalizumab injection	16
Four months after last omalizumab injection	16
Five months after last omalizumab injection	16
Six months after last omalizumab injection	16

3. Discussion

Although cold urticaria is among the most common forms of physical urticaria, its pathophysiology is still largely unknown, despite the likely significant role played by the mast cells activated by Immunoglobulin E (1, 8).

The activation and degranulation of the mast cells lead to the formation of wheals and angioedema. Histamine and other liberated mediators induce vasodilatation and increased permeability, with a consequent edema of the superficial, and/or deep dermis and the subcutis.

In patients with chronic urticaria, the degranulation of cutaneous mast cells would seem to involve autoimmune mechanisms, of which two types are identified.



Figure 1. A cold stimulus is placed on the forearm of the patient for five minutes. The manifestation of an immediate coalescent wheal is indicative of cold urticarial.

In the first type, degranulation takes place due to the binding of IgE autoantibodies to the high-affinity receptor

of the mast cells and occurs after the cross-linking of the autoallergens; for example, the Anti-thyroperoxidase and

Anti-IL-24 (13, 14).

In the second type, mast cell degranulation is induced by IgG autoantibodies directed against the high-affinity IgE receptor.

On mast cell degranulation in cold urticaria however, even less is known, but in this case the involvement of auto-immune mechanisms is also hypothesized (1).

It is certain that, also in this case, a key role is played by the activated mast cells and the consequent release of inflammatory mediators such as histamine.

Mast cell degranulation is modulated by many different signals among which the most important ones are neuropeptides, complementary factors, factors associated with pathogens, as well as drugs and food in intolerant subjects.

The causes of the mast cell activation and degranulation in the chronic inducible urticaria (CindU) are still uncertain: one of the most accredited hypotheses is once again that of an autoimmune- or, more specifically, autoallergic-mechanism.

Some forms of CindU including the cold one are transferable, and it is assumed that the transferable serum factor is represented by IgE. It is shown that desensitization (that in some cases of cold urticaria is effective) does not work through the depletion of mast cells or the mediators released by the latter, but through a reduction of the activation signal of the mast cells.

Although little is known about the actual pathogenic mechanisms of cold urticaria, it is hypothesized that either specific IgE antibodies react against skin antigens (auto-antigens) that would reveal upon a decrease in temperature; or, in the same conditions, circulating IgG (or IgM) auto-antibodies would bind to IgE or to its specific FcεRI on the cutaneous mast cells inducing the release of histamine and other inflammation mediators.

After exposure to cold, in the mast cells of the patients signs of degranulation are observed, and there is an increase in the serum levels of histamine and other mediators such as tumor necrosis factor (TNF)-α and prostaglandin D2 (PGD2), a chemotactic factor for neutrophils, and the activation factor of lipid-like platelets (PAF-like lipid).

In some patients, the association with hematological disorders and cryoglobulinemia is described, and a relationship with bacterial, viral, and parasitic infections is observed, while in some individuals the onset of cold urticaria appeared to be resulting from the use of drugs (Oral Contraceptives, Griseofulvin, ACE-inhibitors, Alprazolam), or from insect or jellyfish bites. Cases occurring after the exposure to a vaccine are also described (15). These apparently secondary forms, however, are extremely rare compared with the total of the cases observed.

According to the numerous possible cold stimuli capable of triggering this type of urticaria, a careful anamnesis is the foundation for a correct diagnosis confirmed by the provocation test, as suggested by the guidelines published by EAACI/GA2LEN/EDF/WAO (11).

Cold urticaria may be a medical emergency, due to the risk of anaphylaxis and oropharyngeal edema.

All the cases highlight the need for an adequate knowledge of the underlying pathogenetic mechanisms and, above all, for an effective and safe therapy that improves the quality of life of patients and protects them from the serious risks they might incur.

Omalizumab is a widely used therapeutic anti-IgE antibody currently indicated to treat moderate to severe persistent asthma and chronic idiopathic urticaria.

It demonstrated robust clinical efficacy, and seems to be promising in a wide range of other allergic diseases. Although it is not yet clear how Omalizumab specifically acts in the various diseases in which it is proven effective, its primary action is to neutralize free serum IgE; therefore, it also reduces the surface levels of IgE on FcεRI-expressing cells, including mast cells and basophils. As IgE surface levels decline on these allergic effector cells, they lose the ability to bind allergen and undergo IgE-dependent activation, and the allergic cascade is interrupted.

The suppression of these cells leads to a reduction of the pro-inflammatory cytokine levels and dendritic cells, lymphocytes, and eosinophils in tissue, and eventually a decrease in the inflammatory state of the whole immune system.

In chronic idiopathic/spontaneous urticaria, several possible mechanisms of action by Omalizumab are assumed (Box 1) that are probably equally effective in cold urticaria (16).

Unfortunately, traditional therapies are often unable to provide adequate and safe responses in this disease, which may become a medical emergency due to the risk of anaphylaxis and oropharyngeal edema, and in any case re-

Box 1. How Omalizumab Could Improve Symptoms in CIU/CSU (16)

Possible Mechanism of Action of Omalizumab in Idiopathic/Chronic Spontaneous Urticaria

- Lowers IgE levels and down-regulates IgE receptors
 - Reduces mast cell releasability
 - Reverses basopenia and improves basophil IgE receptor function
 - Reduces IgG auto-antibody activity against FcεRI and IgE
 - Reduces IgE auto-antibody activity against unknown auto-antigen
 - Reduces any intrinsically abnormal IgE activity
 - Decreases the involvement of coagulation
-

duces the quality of life of the affected individuals that are forced to significantly limit their normal activities (17-19).

Since the symptoms are triggered by the exposure to cold, which is difficult, if not altogether impossible, to avoid in everyday life, a safe and effective therapy appears to be essential.

The satisfactory response to Omalizumab in the current study patient, after the failure of previous standard therapeutic strategies, confirmed the effectiveness of this molecule to treat cold urticaria, which despite what reported in several studies, is not yet recognized and authorized by the competent health authorities to treat this condition.

A strength of the current study was certainly the confirmation of the effectiveness of Omalizumab to treat cold urticaria already highlighted in other studies that represent a great opportunity for patients, and its weak point was that it was a simple case report and controlled clinical trials on a large series of cases are needed to better define the therapeutic potential of the drug.

Based on the authors' experience, and on what was reported in the literature, Omalizumab can be an effective and safe therapeutic alternative to treat cold urticaria.

Despite the effectiveness shown by Omalizumab in many cases of physical urticaria refractory to conventional therapies, (8,19,20) a certain proportion of subjects remain that do not respond satisfactorily, and it is, therefore, necessary to study more thoroughly the mechanism of action of the drug in such conditions in order to select the patients subjected to treatment and establish with confidence the appropriate doses of the drug and the duration of the treatment. In addition to clarifying the potential of Omalizumab to treat the resistant forms of physical urticaria, these investigations also pave the way for further indispensable therapeutic pathways.

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Table 3. Comparison Between the Present Case and Those Found on Pubmed with Indication of the Most Significant Variables, Data, and Differences

Author Name	Case/Symptoms	Comorbidity	City and Country	Journal Name	Publication Date	Patient Age	Patient Gender	Response to Standard Therapy	Response to Omalizumab	Relapse After Omalizumab
Boyce	Systemic symptoms on immersion in ocean water	Asthma	Boston, MA 02115, USA	J Allergy Clin Immunol	2006	12	Female	Unsatisfactory response	Marked improvement	Not known
Metz	Unavailable data	Unavailable data	Berlin, Germany	Int Arch Allergy Immunol	2011	Unavailable data	Unavailable data	Unsatisfactory response	Complete symptom control	Not known
Brodská	Case 1: Recurrent itchy and painful rash in cold-exposed areas/case 2: Diffuse urticaria with shortness of breath and dizziness occasionally, after cold exposure	Case1: Chronic hepatitis B and urothelial cell carcinoma 6 years before/Case 2: None	Zurich, Switzerland	Case Rep Dermatol	2012	53 and 30	Females	Unsatisfactory response	Case 1: Complete response/case 2: Incomplete symptom control	Not known
Le Moing	Unavailable	Unavailable	Lille, France	J Am Acad Dermatol	2013	66/42/21	Females	Unsatisfactory response	Complete response after 4/6/5 injections	Not known
Metz	Unavailable	Two cases: one with concomitant cholinergic urticaria	Berlin, Germany	JAMA Dermatol	2014	Unavailable	Unavailable	Unsatisfactory response	Complete response on retreatment with omalizumab	Not known
Alba Marín	Widespread urticaria, a lack of energy, and a reduced level of consciousness	None	Alzira, Spain	J Invest Allergol Clin Immunol	2015	2	Male	Unsatisfactory response	Complete response	Not known
Ghazanfar	5 cases	Unavailable	Copenhagen, Denmark	Br J Dermatol	2016	Unavailable	Unavailable	Unsatisfactory response	2 of 5 complete response	Not known
KISIKONLIS	5 cases/four of them anaphylactic reaction; one generalized urticaria	Unavailable	Athens, Greece	Pediatr Allergy Immunol	2016	Unavailable	Females	Unsatisfactory response	2 of 5 complete response	Not known
Metz	31 cases	Unavailable	Berlin, Germany	J Allergy Clin Immunol	2017	Unavailable	Unavailable	Unsatisfactory response	4 of 10 (40%) complete response after omalizumab 150 mg/4 of 9 (44%) complete response after omalizumab 300 mg	Not known
Present case	Urticaria only affected the body areas in contact with the cold	None	Teramo, Italy	Iranian Red Crescent Medical Journal	2018	52	Female	Unsatisfactory response	Complete symptom control	To date no recurrence