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# Treatment of Severe Cold Contact Urticaria with Omalizumab: Case Reports

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## Key Words

Anti-immunoglobulin E · Cold contact urticaria · Omalizumab · Physical urticaria

## Abstract

We report 2 patients with cold urticaria with different response to treatment with omalizumab (Xolair®). Cold contact urticaria (CCU) is a common subtype of physical urticaria. It is characterized by the development of wheal and/or angioedema within minutes after cold contact. Clinical manifestation of CCU can range from mild, localized whealing to life-threatening anaphylactic shock reactions. Omalizumab has been described to be useful in cases of chronic urticaria and may be an interesting option for treatment of CCU. We describe one patient with significant and long-lasting improvement of symptoms and one without any improvement after anti-immunoglobulin E therapy. In our case reports, we want to highlight that there is still a small group of patients without benefit from omalizumab treatment. It is necessary to identify this minor subgroup of patients where omalizumab does not represent an effective treatment possibility.

## Introduction

Cold contact urticaria (CCU) accounts for approximately 3% of all cases of chronic urticaria [1]. Among all physical urticarias, CCU represents the second most common subtype after symptomatic dermographism [2]. CCU is characterized by development of wheal and/or angioedema within minutes after cold contact. CCU patients are also at risk of anaphylaxis or oropharyngeal edema. Acquired CCU is mostly idiopathic or can be secondary in cryoglobulinemia, infectious diseases, etc.

Current guidelines for the symptomatic treatment of CCU recommend a stepwise approach beginning with the classical dose of nonsedating H<sub>1</sub>-antihistamines (nsAHs), then increasing the doses of nsAHs up to 4-fold if symptoms persist before changing to a different nsAHs. In very severe cases also other therapeutic options such as

cyclosporin A or oral steroids might be used [3]. The goal of the treatment of urticaria is determined by complete symptom control. It has been previously shown that omalizumab treatment can be safe and effective in patients suffering from recalcitrant physical urticarias such as cold urticaria [4].

## Case Reports

We report different effects of anti-immunoglobulin E (IgE) therapy in 2 patients with cold contact urticaria, both nonresponsive to high doses of nsAHs.

### *First Case Report*

A 53-year-old woman suffered from severe, treatment-refractory cold contact urticaria. Before anti-IgE treatment, the patient had been affected by recurrent itchy and painful rash in the face and other cold-exposed areas for 4 months. Raised, erythematous, intensely pruritic skin lesions typically developed within minutes after exposure to low temperatures, especially after contact with cold air or cool water. She did not tolerate ingestion of cold drinks and foods; she experienced itching of the lips and tongue. There were no associated symptoms, such as fever or arthralgia. Progressing symptoms limited her outdoor activities in the cold and also food choices. She has received several unsuccessful therapies, including various sedating and nonsedating antihistamines, and intermittent oral steroid treatments. Before anti-IgE treatment, cold provocation test was performed. An ice cube applied to the skin resulted in the development of massive wheal and redness within 3 min after removal. Her medical history included chronic hepatitis B. Hepatitis serological marker (anti-HBs) was positive. Furthermore, she had undergone surgery for urothelial cell carcinoma 6 years previously, and was currently without any urological problems. Other relevant concomitant diseases were excluded. No family members had cold-induced rashes. Before anti-IgE therapy was initiated, the patient's total IgE was 207 kU/l. The patient received a subcutaneous dose of 300 mg/month of omalizumab (added to a stable dose of H<sub>1</sub>-antihistamine). Omalizumab was administered according to the US Food and Drug Administration-approved dosing table for the treatment of asthmatic patients, determining the omalizumab dose by body weight and total IgE levels [5]. The patient reported significant improvement of symptoms already within 1 week after the first injection. Omalizumab was well tolerated, without any adverse effects. After 4 months with complete symptom control, anti-IgE therapy was stopped. At the last follow-up, 5 months after the last application of omalizumab, the patient is currently still free of symptoms. Cold provocation test did not lead to any development of urticarial rash. In case of recurrence of urticaria symptoms, we plan to restart anti-IgE therapy.

### *Second Case Report*

A 30-year-old woman presented with severe cold intolerance with urticarial rash for 1 year. Symptoms were induced also by cold provocation test. Cold exposure was extremely disabling for her. The patient experienced diffuse urticaria with shortness of breath and dizziness occasionally. No evidence for an underlying disease (e.g. infection, cryoglobulinemia) was found. Her personal and family history was negative. Before anti-IgE therapy was initiated, the patient's total IgE was 20.8 kU/l. The patient did not respond to oral antihistamine treatment including 4-fold dosage. Therefore treatment with 300 mg omalizumab subcutaneously every 4 weeks was initiated. The patient repeatedly reported fatigue and somnolence all day long after administration of omalizumab. Unfortunately, anti-IgE therapy resulted in only incomplete symptom control. Due to adverse events and insufficient efficacy, omalizumab treatment was discontinued after 8 months. Cyclosporin A treatment was initiated with 200 mg daily, combined with H<sub>1</sub>-antihistamine. Due to headaches reported by the patient, the dosage of cyclosporin A was reduced to 150 mg daily. At the last follow-up, the patient still has not achieved complete remission. The patient has also received an emergency kit with oral corticosteroid, antihistamine and an adrenaline injector.

## Discussion

Cold contact urticaria accounts for approximately 3% of all cases of chronic urticaria [1]. Among all physical urticarias, CCU represents the second most common subtype

after symptomatic dermographism [2]. CCU is characterized by the development of wheal and/or angioedema within minutes after cold contact. Extensive cold contact of large areas of skin may lead to systemic reactions such as generalized urticaria, dyspnoea, tachycardia, hypotension and loss of consciousness [6]. Severe CCU has a significant impact on the patient's quality of life both in a physical and psychological sense [7].

The onset of CCU symptoms may occur at any age but shows a peak in young adults and a weak predominance in women [6]. The symptoms of all physical urticarias are caused by the activation of mast cells and by their release of proinflammatory mediators. However, it is largely unknown how and why mast cells are activated in physical urticaria, i.e. which signals are responsible for mast cells activation [8]. Although no underlying causes are detectable in most CCU patients, an association of CCU with cryoglobulinemia, hematologic disorders has been described in a small subset of patients [9]. Also, a link between CCU and various viral, parasitic, or bacterial infections could be observed. Genomic deletions in *PLCG2* were recently found in 3 independent families with lifelong cold urticaria [10]. Wanderer et al. [6] proposed a classification scheme for cold urticaria based on the severity of reactions ([table 1](#)).

It is important to note that anaphylactic reactions are very common in patients with cold urticaria. These occur most often during water immersion [11]. Patients who experience oropharyngeal reactions to cool liquids or foods (most commonly manifested as lip swelling) are said to be more likely to experience systemic reactions [4].

CCU must be distinguished from a cold-induced form of cholinergic urticaria [12]. This disorder should be suspected in individuals who have typical multiple small urticarial lesions only when exercising in the cold. Cold-induced cholinergic urticaria is not associated with positive cold provocation test [4]. In a small percentage of cases, cold urticaria is associated with the presence of a range of serum cryoproteins. The presence of a cryoprotein can reflect an underlying diagnosis of essential mixed cryoglobulinemia, hepatitis, autoimmune disease, or lymphoma [4]. Cryoproteins were identified in fewer than 10% of adults in a large series [11].

Avoidance of critical cold exposure should be recommended [3] but is often impossible. Symptomatic treatment of choice is the use of nsAHs [3]. In patients with severe CCU who continue to experience symptoms despite up-dosing of nsAHs, the concomitant use of leukotriene receptor antagonists or H<sub>2</sub> blockers has been described [13]. Also the successful use of cyclosporin A and anti-IgE therapy in CCU has been reported [4, 14]. Patients with a history of anaphylaxis or systemic symptoms should receive an emergency kit containing an adrenaline injector, oral corticosteroid and antihistamine [11].

Omalizumab is a recombinant humanized monoclonal antibody against IgE. It is approved for the treatment of moderate-to-severe persistent asthma in patients with a positive skin test response or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (in the United States) or inhaled corticosteroids plus a long-acting inhaled  $\beta_2$ -agonist (in Europe) [5]. Omalizumab blocks the binding of IgE to the Fc $\epsilon$ RI receptor on the surface of target cells, including mast cells and basophils, thus reducing receptor expression and the

release of inflammatory mediators [15]. Four proof-of-concept trials investigated omalizumab in patients with chronic spontaneous urticaria who remained symptomatic despite antihistamine therapy [16–19]. It is known that approximately 30% to 50% of patients with chronic idiopathic urticaria produce IgG autoantibodies against either IgE or its high-affinity receptor (FcεRI) [20]. A subgroup of patients with chronic spontaneous urticaria exhibits IgE antibodies directed against autoantigens, such as thyroperoxidase [19]. All four studies showed that omalizumab significantly improved urticaria activity scores with rapid onset of effect which persisted for the duration of treatment [16–19]. A dose-finding study has demonstrated that 300 mg omalizumab are as efficient as 600 mg and superior to 75 mg [16]. Currently large multi-center phase III studies are ongoing to investigate the efficacy and safety of omalizumab in CIU (ClinicalTrials.gov identifier: NCT01292473).

It has been previously shown that omalizumab treatment can be safe and effective in patients suffering from recalcitrant physical urticaria such as cold contact urticaria [4]. Also other cases of successful use of omalizumab in physical urticaria such as solar urticaria [21] and pressure urticaria [22] have been described. In [table 2](#) we summarize those patients with cold contact urticaria treated with omalizumab.

According to the summary of omalizumab product characteristics, the most commonly observed adverse reactions are injection site reactions, headache, pyrexia and upper abdominal pain [5]. Most of the reactions are mild or moderate in severity and quite rare (about 7%) [23]. Fatigue described by our patient is defined as uncommon adverse event ( $\geq 1/1,000$  to  $< 1/100$ ) [5]. In general, however, omalizumab is well tolerated as has been learned from the use of omalizumab in large cohorts of adult patients [23] and children [24] suffering from allergic asthma.

Up until now, no clear indications on possible responders of CCU patients with omalizumab or useful dosage and length of therapy can be given. From our 2 patients case 1 was responding very fast (within 1 week) and had a long-lasting improvement. On the other hand case 2 did not respond in a satisfactory manner and also suffered from a variety of side effects. However, it has to be considered that this patient also did not respond very well to cyclosporin A and also suffered from a broader spectrum of side effects with this drug.

## Conclusions

Many case reports have already shown the beneficial effect of omalizumab in patients with recalcitrant physical urticaria [4, 21, 22, 25]. In addition to previously published reports, our case suggests that omalizumab may be an effective, rapid and safe treatment option in patients with cold contact urticaria who do not sufficiently respond to standard therapy as recommended by existing guidelines. Still there is a small group of patients without sufficient response to omalizumab. Further research is necessary to clarify the mechanism of action of omalizumab in patients with CCU. Future trials, including longer durations of treatment, should fully evaluate the potential of this agent in the treatment of all recalcitrant physical urticarias. Another focus of interest will be to identify the patients who will not profit from omalizumab treatment [8].

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**Table 1.** Classification scheme for cold contact urticaria [6]

Severity of reactions	
Cold urticaria	type 1 reactions confined to the area of skin that came into contact with the cold
	type 2 generalized urticaria not associated with cardiovascular or respiratory symptoms
	type 3 generalized urticaria associated with cardiovascular or respiratory symptoms

**Table 2.** Characteristics of cold contact urticaria patients treated with omalizumab

Pa-tient	First author, year	Sex	Age years	Duration of CCU	Previous medication	Omalizumab dosage	Successful use
1	Boyce [4], 2006	woman	12	2 years	high-dose nsAH, montelukast	375 mg/ 2 weeks	yes
2	Metz [8], 2011	man	19	NA	high-dose nsAH	150 mg/ 4 weeks	yes
3	our patient – case 1, 2012	woman	53	4 months	high-dose nsAH, occasional oral steroids	300 mg/ 4 weeks	yes
4	our patient – case 2, 2012	woman	30	1 year	high-dose nsAH	300 mg/ 4 weeks	no

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