

*Case study***Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE**Joshua A. Boyce, MD *Boston, Mass*

A case of a girl who presented at age 12 years with idiopathic cold urticaria is described. Her reactions to the cold became progressively more severe over a period of approximately 2 years, despite therapy with H1 antagonists and a type 1 receptor for cysteinyl leukotrienes receptor antagonist. She began to experience systemic symptoms on immersion in ocean water. She was atopic and had moderate persistent asthma. A trial of anti-IgE resulted in complete resolution of her urticaria and its associated manifestations. These findings should prompt a reexamination of the potential pathogenetic role played by IgE and its high-affinity receptor on mast cells in idiopathic cold urticaria. (*J Allergy Clin Immunol* ■■■■;■■■;■■-■■.)

Key words: *Urticaria, anaphylaxis, mast cells, IgE*

CASE PRESENTATION

A 12-year-old girl presented for evaluation of a repetitive pruritic rash occurring reproducibly after exposure to cold temperatures. She had been in her usual state of health until several months after moving to the Northeastern United States from Florida. Episodes of rash initially were typified by raised, erythematous, intensely pruritic skin lesions that were confined to cold-exposed areas, especially after contact with cool water or cold surfaces. The lesions developed within minutes, particularly with re-warming of the exposed skin. They were evanescent, disappearing within 30 to 60 minutes of ingestion of diphenhydramine, and left no bruising or discoloration in their wake. There were no associated constitutional symptoms, such as fever or arthralgias. Over a roughly 2-year

Abbreviation used

FCAS: Familial cold autoinflammatory syndrome

period, the episodes began to occur with progressive frequency and severity and began to include lesions developing on cold air exposure. On one occasion, the patient experienced diffuse urticaria, shortness of breath, and dizziness while swimming in the ocean. These symptoms resolved with administration of diphenhydramine, recumbence, and deep breathing. Initially, she could tolerate the ingestion of cold liquids and foods, but gradually began to experience itching of the lips, tongue, and pharynx and occasionally a “full” feeling at the back of her throat during such ingestions. Her symptoms had progressed to a point that precluded outdoor activities in the cold and limited her ingestion of cold or frozen foods.

Her past medical history was noteworthy for asthma, with symptoms dating to toddlerhood. Exacerbations of asthma had occurred several times annually, generally in association with upper respiratory tract infections. Additionally, she consistently experienced coughing, chest tightness, and occasional wheeze with high levels of physical activity and with cold air inhalation. She was hospitalized once for asthma at the age of 10 years, requiring several days of inpatient treatment with systemic glucocorticoids and bronchodilators for resolution of the exacerbation. She also had persistent symptoms of nasal obstruction, as well as nasal itching and sneezing in the springtime. She was maintained on fluticasone (250 µg) and salmeterol (50 µg) at 1 puff twice daily, plus montelukast (5 mg) daily for asthma control. She also used fluticasone nasal spray (25 µg) on each side daily and cetirizine (10 mg at bedtime). Percutaneous allergy testing had been performed in the past, with positive reactions to cat, dust mites, and tree pollens. Desensitizing shots were attempted but were discontinued because of a severe systemic allergic reaction.

Review of systems was noteworthy for a lack of evident cutaneous or gastrointestinal reactions to foods. There were no night sweats, joint aches, fever, or weight loss. There had been no transfusions. Family history was noteworthy for 2 siblings with asthma and a mother with allergic rhinitis. No family members had cold-induced rashes.

Physical examination revealed an alert, well-appearing girl in no evident distress. Vital signs were unremarkable.

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Height and weight were at the 50th to 75th percentiles and had shown no deceleration. Nasal examination revealed boggy pale mucosa. Lymph nodes were normal in size. The chest was clear to auscultation. There were no cardiac murmurs. The abdomen was soft, and there was no organomegaly. The digits were not clubbed, and there were no nail bed or joint abnormalities. Pulmonary function showed a forced vital capacity of 2.85 L, an FEV₁ of 2.43 L, and a midexpiratory flow rate of 2.66 L/s (corresponding to 106%, 102%, and 90% of predicted value).

An ice cube applied to the skin of the right forearm for 5 minutes resulted in the development of a massive wheal (10 cm) and flare (25 cm) within 3 minutes of removal.

DIFFERENTIAL DIAGNOSIS

This otherwise healthy 11-year-old presented with cold-induced cutaneous reactions consistent with urticaria. These episodes were steadily progressive in frequency and severity over a roughly 2-year period. Systemic symptoms (chest tightness) had occurred with cool water immersion, and symptoms of oropharyngeal pruritus and possibly pharyngeal edema had ensued with ingestion of cool liquids. The result of an "ice cube test" was floridly positive. She was atopic and had moderate persistent asthma, as well as both perennial and seasonal asthma. The differential diagnosis includes (1) "idiopathic" cold urticaria, (2) cold urticaria in association with abnormal serum proteins (cold agglutinins, cryoglobulins, and cryofibrinogen), (3) cold-induced cholinergic urticaria, and (4) familial cold autoinflammatory syndrome (FCAS).

LABORATORY WORKUP

Complete blood cell revealed a hemoglobin value of 13.5 g/dL, a hematocrit value of 41%, and a total white cell count of 7500/mm³. Differential showed 51% neutrophils, 37% lymphocytes, 8% monocytes, and 4% eosinophils (total eosinophil count of 300/mm³). The erythrocyte sedimentation rate was 4. The total IgE level was 1078 IU/mL. Cryoglobulins, cryofibrinogen, and cold agglutinins were not detectable.

TENTATIVE DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS

This patient's clinical presentation was consistent with the diagnosis of idiopathic cold urticaria.¹ Cold urticaria accounts for approximately 3% of all cases of chronic urticaria.² Both young adults and children are affected,^{2,3} and cases have been documented in infants as young as 6 months.³ In a series of 30 pediatric patients, the median age of onset was 7 years (range, 0.5-14.5 years).³ The course tends to be chronic, with most patients experiencing symptoms for years, regardless of the age of onset.^{2,3} Some series identify a female predilection of

roughly 2 to 1.^{2,4} Atopy (as defined by positive skin prick test responses) might be more common in patients with cold urticaria than in many other forms of chronic urticaria. Among 19 children tested in the pediatric series, 16 had positive skin test responses to at least one allergen.³ In this series 14 of the 30 patients also carried the diagnosis of asthma. In a series of adults, a family history of atopy was identified in approximately 70%.² Thus although no proved causative link between atopy and cold urticaria can be inferred at present, an association seems plausible.

Cold urticaria must be distinguished from a cold-induced form of cholinergic urticaria.⁵ The latter disorder should be suspected in individuals who have typical lesions (multiple small urtications) only when exercising in the cold. Cold-induced cholinergic urticaria is not associated with urtication on ice cube test. FCAS, formerly known as familial cold urticaria, is a rare condition characterized by fever, rash, and arthralgias elicited by exposure to cold,⁶ although the immediate response to an ice cube test is negative. This syndrome, inherited as an autosomal dominant trait, is associated with mutations in a novel gene (*CIAS1*) localized on chromosome 1q44 encoding a pyrin-like molecule.^{7,8} The lack of a family history of cold-induced cutaneous reactions in this case and the absence of fever and arthralgias essentially rules out FCAS.

Cold urticaria is typically induced by contact with water, cold air, or cold surfaces, often on rewarming of the exposed area. Wanderer et al¹ proposed a classification scheme for cold urticaria based on the severity of reactions. Type 1 refers to reactions confined to the area of skin that came into contact with the cold. Type 2 refers to generalized urticaria not associated with cardiovascular or respiratory symptoms. Type 3 refers to patients having one or more episodes associated with symptoms and signs indicative of respiratory or cardiovascular compromise. It is important to note that systemic anaphylactic reactions are common in patients with cold urticaria, occurring in roughly 1 in 3 patients. These occur most often during water immersion.²⁻⁴ The cardiovascular system is the most common extracutaneous site of reaction, followed by reactions involving the respiratory (wheeze and dyspnea) and gastrointestinal (cramping and vomiting) systems. 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. Deaths have been reported, most commonly in association with immersion in water ("swimmer's death").⁹ Thus it is imperative that patients with cold urticaria be cautioned against immersion in water and be equipped with injectable adrenalin.

In a small percentage of cases, cold urticaria is associated with the presence of a range of serum cryoproteins. Cryoglobulinemia, cryofibrinogenemia, and cold agglutinins have all been reported.⁴ The presence of a cryoprotein can reflect an underlying diagnosis of essential mixed cryoglobulinemia, hepatitis, autoimmune disease, or lymphoma. The cryoprotein might be pathogenetic because they can confer the cold reaction on transfer of serum and can fix complement on precipitation *in vitro*.^{9,10}



FIG 1. Effect of omalizumab on skin reactivity to locally applied cold stimulus (ice cube test): wheal-and-flare response observed 10 minutes after a 5-minute application of an ice cube to the right forearm before treatment (*left*) and again after 6 months of treatment with anti-IgE (*right*).

suggesting a disease mechanism involving the generation of anaphylotoxins. Functional autoantibodies against IgE have been described, both of the IgM and IgG classes,¹¹ which can also induce the reaction on passive transfer of patient serum to unaffected individuals. An array of infectious diseases have been associated with cold urticaria, including toxoplasmosis,¹² EBV,¹³ *Helicobacter pylori*,¹⁴ hepatitis C,¹⁵ and HIV.¹⁶ Although the presence of cryoproteins in a subset of patients can imply an underlying systemic illness or infectious cause, it is important to note that the vast majority of patients with cold urticaria lack such cryoproteins. Cryoproteins were identified in fewer than 10% of adults in a large series² and were not detected in any of the 30 children reported in the pediatric series.³ Thus almost all otherwise healthy patients with cold urticaria have an idiopathic variant.

Mast cells and their products are implicated in the pathophysiology of idiopathic cold urticaria. A study of 6 such patients used an “immersion challenge,” in which a hand was immersed into ice water for 4 minutes to elicit a localized response, followed by serial measurements of histamine in blood drawn from the draining brachial vein. All patients experienced an increase in plasma histamine concentrations, peaking at 4 to 8 minutes after removing the hand from ice water, and this coincided in some patients with a decrease in blood pressure.¹⁷ In addition to histamine, cold challenge has been reported to elicit the local release of cysteinyl leukotrienes¹⁸ and prostaglandin D₂.¹⁹ Treatment with H₁ antagonists produces at least partial improvement in the majority of patients,²⁻⁴ although some remain refractory to such intervention at standard doses. Cyprohepatine (Periactin) is particularly effective.²⁰ One study reported efficacy for zafirlukast, an antagonist of the type 1 receptor for cysteinyl leukotrienes.²¹ Collectively, these studies indicate that mast cell activation occurs as a feature of cold urticaria and that mast cell products play a causative role in producing the reactions. A potential role for an IgE-dependent

mechanism for cold urticaria was inferred from earlier serum transfer studies. Hauser et al²² reported on 4 patients with cold urticaria who all had a transferable factor that was heat labile and could be removed by using an IgE immunoaffinity step. Kaplan et al¹⁷ demonstrated a transferable serum factor consistent with IgE in one patient. Although such studies are consistent with a role for IgE (which might relate to the frequent association with atopy), it is unclear as to the mechanisms by which IgE-dependent mast cell activation can be provoked by cooling of the skin microvasculature in such cases.

DIAGNOSIS AND DISCUSSION OF MANAGEMENT PLAN

The clinical history of the reactions, the absence of systemic illness and cryoproteins, and the positive ice cube challenge test response (application of an ice cube to the forearm for 5 minutes, followed by 10 minutes of observation) confirmed the diagnosis of idiopathic cold urticaria in this patient (type 3 according to the classification of Wanderer et al¹). Despite increasing doses of cetirizine (to 10 mg twice daily), concomitant use of montelukast, and trials of other antihistamines, including cyproheptadine, the patient continued to experience episodes of increasing frequency and severity. The progressive nature of her symptoms and the fact that she continued to have asthma exacerbations in spite of moderate-dose inhaled steroids, long-acting β -agonists, and montelukast, led to an empiric trial of omalizumab (anti-IgE; 375 mg every 2 weeks). After her second infusion, she was able to tolerate cold liquids with only mild palatal pruritus. After roughly 2 months of treatment, exposure to cold air and immersion in ocean water produced only mild cutaneous pruritus and no urticaria, and after 5 months of treatment, even these symptoms disappeared. Ice cube test responses reverted to negative (Fig 1). She was able

to resume all activities, including skiing and swimming. The patient's symptoms returned when she missed 2 doses of omalizumab but again remitted after her next infusion. Additionally, control of both her asthma and her rhinitis improved dramatically. She was able to tolerate a reduction in her fluticasone dose (100 μ g twice daily) without recrudescence of symptoms. She discontinued her nasal steroids, antihistamines, and montelukast without incident.

This is the first report of a clinical response to anti-IgE treatment of a case of severe idiopathic cold urticaria. The marked improvement supports the purported pathogenetic role for IgE in cold-induced mast cell activation that had been inferred from earlier serum transfer studies of patients with idiopathic cold urticaria.^{17,22} The established efficacy of anti-IgE in the treatment of allergic asthma²³ and allergic rhinitis²⁴ putatively reflects the depletion of free IgE from the serum and tissue, leading ultimately to reduced binding of IgE to its high-affinity surface receptor, Fc ϵ RI. Because occupancy of Fc ϵ RI by IgE determines the levels of surface Fc ϵ RI expression, this leads to a rapid depletion of both cell-bound IgE and surface Fc ϵ RI expression on blood basophils²⁵ and a more gradual depletion of these proteins from skin mast cells.²⁶ The kinetics of depletion of Fc ϵ RI from mast cells resident in other mast cell-rich organs (eg, the gastrointestinal and respiratory tracts) has not been established. Studies on additional patients with idiopathic cold urticaria will be necessary to establish the generalizability of clinical efficacy of anti-IgE observed in this case and to define the kinetics of the response in terms of clinical reactions, mediator release, and the skin response to ice cube challenge. Such studies might ultimately permit recognition of the identity of antibody specificity and putative mechanism of disease.

SUMMARY

Although cold urticaria is associated with cryoproteins and associated underlying systemic disease in a small patient subgroup, most patients have an idiopathic variant. This is especially true for children. The diagnostic workup should be tailored based on patient age and associated symptoms and signs. Treatment with H1 antagonists is helpful to most, but not all, patients and reflects the involvement of other mediators, including cysteinyl leukotrienes. The risk of mortality with water immersion emphasizes the importance of patient education and the availability of injectable adrenalin. The unexpected successful treatment with anti-IgE in the severe case reported here provides pathophysiologic insight, as well as a potential treatment option for patients with severe disease at risk for mortality.

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