

Case Report

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Five Cases of Antihistamine-Refractory Chronic Inducible Urticaria Treated with Omalizumab

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Abstract

Chronic inducible urticaria (CIndU) is a common inflammatory skin disorder. Currently there are no recommended guidelines on using anti-IgE antibody, omalizumab in CIndU. We describe five cases [three cases of IgE mediated immunological contact urticaria, one case of delayed pressure urticaria (DPU) and one case of Symptomatic Dermographism (SD)]. Four of these cases achieved complete symptom control (rapid responder) (UAS 7 improvement: Case 1- 29 to 4, Case 2- 30 to 5, Case 3- 32 to 4 and Case 5- 30 to 5) while one case of DPU was a slow responder (Case 4- UAS 7 improved from 28 to 11). Three cases of IgE mediated immunological contact urticaria had higher baseline total IgE with positive skin prick test and specific IgE to food and aero-allergens, signifies the successful response to omalizumab. Once disease control is achieved, the strategy for duration of the omalizumab therapy has not been determined. We hypothesize that omalizumab given at monthly doses, is a safe, effective and well tolerated therapeutic option in antihistamine-refractory CIndU.

Keywords: Chronic inducible urticaria (CIndU); Physical urticarial; Chronic Spontaneous Urticaria (CSU); Contact urticaria; Dermographism; Delayed pressure urticarial; Anti-IgE; Omalizumab; Seven day Urticaria Activity Score (UAS 7)

Introduction

Chronic inducible urticaria (CIndU) is a common inflammatory skin condition affecting 0.5% of the population, characterized by the recurrence of itchy wheals and/or angioedema that lasts more than 6 weeks and is induced by physical stimuli (dermographism, delayed-pressure urticaria, exercise-induced urticaria, cold urticaria, heat urticaria, solar urticaria, and vibratory urticaria) and non-physical stimuli (cholinergic urticaria, contact urticaria, and aquagenic urticaria) [1].

Symptomatic Dermographism (SD) and Delayed Pressure Urticaria (DPU) are found in combination with CSU in 10% to 50% of patients and up to 36% of patients with CSU have been reported to react concomitantly to physical trigger tests [3]. The diagnosis of CIndU is made on the basis of the patient history and the results of provocation tests, which make use of the relevant stimuli in controlled settings [2].

Contact urticaria is a subtype of CIndU, wherein symptoms range from a localized wheal or flare reaction to generalized urticaria and anaphylaxis appears following contact between an exogenous agent and the skin or mucosa. Diagnosis of contact urticaria is based on clinical presentation and patient history, which includes the time and duration of onset, symptoms, distribution, family history, drug use, previous allergies or anaphylactic reaction to insect stings and stress. Diagnosis is made by a) open test on the unaffected skin, b) prick test, if the open test is negative, c) Scratch test for non-standardized allergens and d) use test. There are two types of this disease: non-immunologic contact urticaria and immunologic contact urticarial [4]. Non-immunologic contact urticaria, the more common type, is an immediate reaction not requiring prior exposure to the substance. The symptoms usually occur only in the area of contact. Common causes are-foods, especially fish, fragrances, flavorings, medicaments, animals, esp. caterpillars, jellyfish, plants, esp. nettles, corals, preservatives, antiseptics, ammonium persulphate. Common sites of contact urticaria are hands, arms and face. Risk factors are occupational-health care workers, food handlers, hair dressers, bankers, dental assistants, agricultural, dairy workers, electronic workers, veterinary workers etc. Immunologic contact urticaria is an IgE-

mediated hypersensitivity reaction occurring in patients previously sensitized to a trigger which can occur through contact with skin or mucus membrane (respiratory or gastrointestinal). The reaction occurs within minutes to hours affecting the skin and other organs. Common causes include house dust mite, dairy products, fruits, nuts, esp. peanuts, meats, sea foods, vegetables, esp. garlic, onion, fragrances, hair care products, medicaments, antibiotics, plant products, esp. latex[1,5,6]. We have three cases of IgE mediated immunological contact urticaria (Cases 1-3).

Delayed-pressure urticaria (or delayed-pressure angioedema)-DPU, is a form of CIndU characterized by a recurrent erythematous and often painful swelling that appears after pressure to the skin which commonly occurs on the hands, feet, trunk, buttocks, legs, and face. The activities that typically induce the symptoms include wearing tight clothes (affecting constricted areas), sitting on a hard surface for prolonged periods, standing, extensive walking (affecting the soles and feet), carrying heavy bags (affecting the palms and hands), or compression against a pillow (affecting the face). Patients often have an associated sense of burning and feel pain, but rarely itching or arthralgia. Lesions may last for 8 to 72 hours and can also be associated with fever, malaise, fatigue, and occasionally chills, headache, and general joint aches. In more than half of the patients (up to 60%), there are other concomitant forms of chronic urticaria, immediate and/or delayed dermatographism, and/or angioedema [7]. Diagnosis of DPU is made by hanging a weight from the patient's arm for 20 minutes; for example, attaching a 5 kg weight to a sling (sand bag test). A 5 kg rod may also be placed across the patient's forearms for 20 minutes. The patient observes the skin for symptoms over the next 24 hours. The delayed appearance of an erythematous palpable swelling confirms the diagnosis [1].

Dermographism (dermographic urticaria) is the most common type; it manifests as though someone has been writing on the skin, mostly occurring after firm stroking, scratching, or pressure on the skin [1]. Symptomatic dermatographism (SD)

manifests with itchy hives that appear in less than 5 minutes and usually last 30 minutes (wheals are associated with an itch that becomes worse at night and with friction stimulated by a trigger: external stimuli, heat, stress, emotion, and exercise). The diagnosis of dermatographism is usually made by observing the clinical response after using moderate pressure to stroke or gently scratch the skin. The site for scratch test is important because areas protected from regular pressure and environmental influences, (e.g., the back) typically are more reactive than more exposed areas (e.g., the buttocks and limbs).

We describe one case of DPU and another case of SD poorly responding to high dose anti-histamine and courses of OCS.

Omalizumab selectively binds to human immunoglobulin E (IgE), thus preventing IgE from binding to its high-affinity receptor (Fc ϵ RI) and reducing the amount of free IgE. This process affects the immunologic cascade of urticaria on several levels, thus reducing receptor expression and the release of inflammatory mediators [8]. Omalizumab provides rapid and effective symptom relief in more than three quarters of an unselected group of 51 patients with CSU and CIndU who had been shown to be unresponsive to H1-antihistamines and, in many cases, to second and third-line therapies as defined by the EAACI/GA2 LEN/EDF/WAO guidelines on the management of urticaria [9,10].

A recent randomized controlled study found that levels of Fc ϵ RI- and IgE-positive cells were higher in patients with CIndU/CSU and normalized after 12 weeks after injection omalizumab therapy when compared with healthy volunteers [11].

Omalizumab may indeed reduce mast cells (MC) releasability, defined as the normalization of 48/80-induced histamine responses or expression of MRGPX2 [9, 12]. This could explain the clinical observation that omalizumab improves symptoms in patients with physical urticaria such as cold-induced or dermatographism as well as in disorders of mast cells (MCs) such as MC activation or idiopathic anaphylaxis in patients with mastocytosis [9, 11].

Case	Age/sex	Duration of disease	Co-morbidities	Type of urticaria	Total IgE (IU/ml)	Previous treatment	Dose & duration of omalizumab	UAS 7 Before	UAS After
1	32 years/M	10 years	HPA suppression (S. cortisol-1.8 ug/dL)	Contact urticaria- latex	175	4-AH1, AH2, LTRA, OCS	150 mg once a month for 11 months	29	4
2	44 years/M	5 years	NIL	Contact urticaria-food	794	4-AH1, AH2, LTRA, OCS	150 mg once a month for 12 months	30	5
3	25 years/M	6 years	NIL	Contact urticaria-Dust	219	4-AH1, AH2, LTRA, OCS	150 mg per month for 4 months	32	4
4	48 years /F	25 years	HPA suppression (S. cortisol-3.01 ug/dL)	DPU	35.9	4-AH1, AH2, Cyclosporine, Mtx, OCS, dapsone	150 mg per month for 28 months	28	11
5	37 years/M	22 years	HPA suppression (S. cortisol-4.9 ug/dL) Hypothyroidism	SD	6.1	4-AH1, AH2, LTRA, OCS	150 mg per month for 11 months	30	5

SD: Symptomatic Dermographism; AH1: First Generation Anti-histamines; AH2: Second generation Anti-histamines; OCS: Oral Corticosteroids; Mtx: Methotrexate; LTRA: Leukotriene Receptor Antagonist; HPA: Hypothalamic Pituitary Adrenal Axis

Table 1: Clinical characteristics of cases 1-5.

Case 1

32 years old male, history of IgE mediated immunological contact urticaria, angioedema and bronchospasm on suspected exposure to latex gloves (SPT negative, use test-positive) and after intake of drugs (NSAIDS and beta lactams) since 10 years with a history of HPA suppression. He had been on oral antihistamines, OCS and montelukast but responded poorly (*UAS 7 was 29*). He was given Inj. Omalizumab 150 mg once a month for 3 months (*UAS 7 improved to 4*) and continued for the next 8 months till complete symptom control (Table 1) (Figure. 1).



Figure 1: Contact urticarial.

Case 2

44 years old male, history of IgE mediated immunological contact urticaria (generalized erythematous wheals with intense itching) with lip and periorbital angioedema on contact after intake of yeast containing products, rice beer, bamboo-shoots, egg, popcorn, tomato, soyabean, coffee, tea, fish since 5 years. He had been taking oral anti-histamines, montelukast, and on & off OCS with no improvement (*UAS 7 was 30*). He was given Inj. Omalizumab 150 mg once a month for 3 months (*UAS 7 improved to 5*) and continued for 9 more months with no recurrence (Table 1).

Case 3

25 years old male, presented with history of IgE mediated immunological contact urticaria on exposure to dust [Skin prick test (SPT) positive with *Dermatophagoides pteronyssinus* 6mm wheal size and *Dermatophagoides farinae* 6mm wheal size] and physical activity (walking, exercise), emotional stress and sun exposure since last 6 years, progressed to allergic rhinitis and intermittent asthma during winter months (Nov-Feb) since 2 years. He responded poorly to high dose of anti-histamines and on & off OCS (*UAS 7 was 32*). He was given Inj. Omalizumab 150 mg once a month for 4 months (*UAS 7 improved to 4*) (Table1). Currently on follow-up.

Case 4

48 years old female, history of recurrent itching with intense burning followed by linear erythematous, edematous wheals over her trunk and extremities at pressure sites like tight clothing (belts, shoulder straps, bra straps) (Figure. 2) and had swelling of the hands after carrying heavy loads like shopping bags, appearing after 3-6 hours since the last 25 years. She had been on anti-histamines, multiple courses of cyclosporin (17 months), methotrexate, oral corticosteroids, dapsone and various indigenous treatment without improvement (*UAS 7 was 28*). History of surgery and chemotherapy for breast cancer 25 years back. She was given Inj. Omalizumab 150 mg per month for 28 months, and slowly improved with the occasional need of anti-histamines (*UAS 7 improved to 11 after 12 months*) (Table 1).



Figure 2: Delayed pressure urticarial.

Case 5

37 years old male, history of hypothyroidism, HPA suppression and severe SD (itching palpable wheals within 10 minutes aggravated in context to usual activities (dressing, tight clothes, some physical activities) since last 22 years (Figure. 3). He had been on effective dose of oral-anti-histamines and OCS on and off for the last 20 years without any improvement (*UAS 7 was 30*). He was given Inj. Omalizumab 150 mg once a month (*UAS 7 improved to 5 after 3 injections*) and continued for 8 months till symptom control (Table 1).



Figure 3: Symptomatic dermographism.

Discussion

CIIndU patients can be treated successfully with up-dosing of H1-antihistamine and addition of other medication such as leukotriene receptor antagonist (LRTA) and H2-receptor blockers, but there are some patients who still suffer from severe symptoms. The current guidelines state that goal for the treatment of these patients has to be complete symptom control. Immunological

contact urticaria is an IgE mediated hypersensitivity reaction in which there is sensitization to antigens through contact with skin or mucus membrane (respiratory or gastrointestinal tract) [1]. The causative agent is of low molecular weight, salt soluble proteins of plant and animal source proteins, usually found in skin care products (cosmetics, soap etc.), dust mites, natural rubber, and latex as seen in our three cases. Whether inhalation route can induce IgE-mediated immunological contact urticaria, needs further studies, like in Baker's asthma and contact urticaria, which is induced by raw wheat flour. Our three patients received high doses of antihistamines (cetirizine and fexofenadine) with on and off courses of OCS, without any improvement in their symptoms.

The diagnosis in these three cases of IgE mediated immunological contact urticaria was based on skin contact with latex gloves; use test-positive (Case 1), mucosal contact [after ingestion of yeast like products (Case 2) and after exposure to dust (Case 3)].

Among five cases, three patients were of IgE mediated immunological contact urticaria and 1 patient of SD achieved complete symptom control with omalizumab except for one patient of DPU which could only achieve partial control. In our three patients, we observed very rapid improvement of the symptoms (*UAS 7 improvement: Case 1- 29 to 4, Case 2- 30 to 5 and Case 3- 32 to 4*) during omalizumab treatment. It signifies that IgE plays an important role in the pathogenesis of IgE mediated immunological contact urticaria. These three cases (case 1-3) have higher baseline total IgE with positive skin test to food and aeroallergens.

In Case 4 of DPU, the diagnosis was based on history and provocation test (sand bag test), performed by the patient. The pathogenesis of DPU remains unknown but increased levels of interleukins (IL-6), TNF-a, and IL-3 have been found. We started omalizumab therapy along with fexofenadine, which provided partial relief but improved slowly after 12 months of omalizumab therapy. The anti-histamine dose was gradually reduced until a standard dose of once a day was maintained. Before omalizumab, the patient presented with UAS 7 of 28 which improved to UAS 7 of 11 after one year.

In case 5 of anti-histamine refractory SD, the diagnosis was made by simplified dermatographic tester that applied graded shearing forces to the skin, thus allowing for the determination of the trigger threshold. A response to dermatographic testing is considered positive if a pruritic palpable wheal of >3 mm width is present within 10 minutes after provocation [13]. This patient achieved almost complete response (absence of wheals after provocation test) after 3 injections of omalizumab which was further continued for 8 months till fexofenadine was stopped.

From our experience of five cases, we hypothesize, omalizumab is a highly effective, rapidly acting and safe for the management of anti-histamine refractory cases of IgE mediated

immunological contact urticaria, DPU, and SD. The author has also reported significant improvement in five cases of CSU and one case of Normocomplementemic urticarial vasculitis (NUV) with omalizumab [14].

We need to characterize the different phenotypes of patients of CIndU who are refractory to standard up-dosing of anti-histamine treatment and search for clinical predictors and accurate diagnostic tests (autoimmune parameters, inflammatory markers). Clinical trials with large patient numbers should be performed to further investigate the use of omalizumab in these cases.

Conclusion

In our five cases, a combination of omalizumab and anti-histamine was effective in the treatment of refractory IgE mediated immunological contact urticaria, DPU, and SD. Omalizumab is associated with rapid and significant improvement of symptom control with quality of life. Whether omalizumab restores immune function and modulates the production of related cytokines and antibodies, more studies are required to investigate the pathophysiology of CIndU.

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