

A case of severe refractory chronic urticaria: A novel method for evaluation and treatment

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ABSTRACT

With cholinergic urticaria (ChU), the ultimate diagnosis often depends on the demonstration of characteristic urticaria by appropriate provocation. Several treatment options may be helpful but traditional options (antihistamines, leukotriene inhibitors, and immunosuppressives) may be exhausted by the refractory ChU patient. Here, we describe such a case. Demonstration of immediate hypersensitivity to autologous sweat skin testing (ASwST) may provide a rationale for use of omalizumab (Xolair, Genentech Novartis, South San Francisco, CA). Patients with severe ChU may have difficulty producing sufficient quantities of sweat for ASwST given that the very effort that produces the sample exacerbates ChU. Generation of sweat by iontophoresis with pilocarpine nitrate can be performed at many large medical centers. The procedure is simple, safe, and produces varying amounts of sweat depending on the individual. This sweat can then be used for ASwST. Our patient had a positive ASwST with appropriate positive and negative controls. Our testing methods were validated by negative ASwST, saline control, and positive histamine control in a nonatopic, nonurticarial control patient. By the patient's second injection of omalizumab, her quality of life score was significantly improved, as were her daily medication scores and exercise tolerance. We describe the first case of a patient with severe refractory ChU who had a positive ASwST by a novel collection method who has been successfully treated with omalizumab. We present a novel tool for the evaluation and demonstration of sweat-specific IgE in ChU patients who are unable to provide sweat by more traditional means.

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Key words: Autologous sweat skin test, cholinergic urticaria, omalizumab, pilocarpine iontophoresis, sweat collection, urticaria, Xolair

CASE PRESENTATION

Chief Complaint

Hives.

History of Present Illness

A 25-year-old woman initially presented in early 2007 complaining of very pruritic red raised bumps with strenuous exercise since 2000. She reported <5-mm pruritic bumps that would coalesce triggered by significant exertion and with other increases in her body temperature, such as hot showers or getting into

a hot car. Over the years, her lesions had become more severe and her exercise tolerance had reduced from 45 minutes before the development of her condition to <5 minutes. By summer 2007, climbing a flight of stairs or physical labor at work would cause her to urticate to the point that she would have to stop what she was doing.

Medical History

Medical history was significant for intermittent seasonal rhinitis and dysmenorrhea.

Physical Examination

The patient rarely had lesions on the days of her clinic visits and her exam was otherwise normal. There was no evidence of dermatographism, hyper- or hypopigmentation, chronic angioedema or other rashes. She had several pictures showing generalized urticaria and facial swelling on different occasions at home, work, and after exercise.

Initial Laboratory and Other Diagnostic Findings

The patient's baseline labs in winter 2007 total serum tryptase were 2 ng/mL, total IgE was 103 IU/mL, and

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ESR was 15 mm/hour. Thyroid stimulating hormone, metabolic and hepatic panels, and CBC were all normal including a normal differential. *Helicobacter pylori* serum antibody was positive.

Clinical Course

The rash progressively worsened to the point of requiring twice-daily cetirizine, ranitidine, fexofenodine, once-daily montelukast, and as-needed hydroxyzine. She described her daily urticarial severity as 8/10 points on a subjective scale with 10/10 off medications or during light exertion. By early 2008, the patient's duties were severely limited and she could not perform her mandatory physical fitness testing. Hyoscyamine was tested twice daily without any beneficial effect, consistent with previous reports.¹ Secondary causes of chronic urticaria (CU) were evaluated as recommended in the CU practice parameter.² The patient received triple therapy for her positive *H. pylori* antibody without improvement in her cholinergic urticaria (ChU). With assistance from her gynecologist, different birth control medications were tested without avail. She was hesitant to test long-term steroids, danazol or immunosuppressant medications.

QUESTIONS

What Is the Differential Diagnosis?

The different diagnosis includes ChU, chronic idiopathic urticaria (CIU), exercise-induced anaphylaxis, food-induced exercise-induced anaphylaxis, mastocytosis, and idiopathic anaphylaxis.

What Additional Laboratory Data or Investigations would be Helpful in Arriving at a Diagnosis?

Additional diagnostic testing could include exercise challenge, hot water bath, intradermal skin testing with methacholine or autologous serum, and/or sweat testing.³⁻⁵

In spring 2007, the patient underwent exercise challenge and developed pinpoint urticaria after several minutes of exertion. Her classic pinpoint urticaria quickly coalesced and she then developed angioedema (Fig. 1) and her forced expiratory volume in 1 second dropped 12.4% from baseline. She received a nebulized albuterol treatment and two doses of epinephrine with rapid symptom resolution. The patient's tryptase after exercise testing in spring 2007 was 8 ng/mL.

The patient's response to exercise was suggestive of the diagnosis but further provocative testing was considered to allow consideration of additional therapeutic options. As such, autologous serum skin testing (ASST) and autologous sweat skin testing (ASwST) were considered. ASST was negative with positive histamine and a negative saline control. We discounted hot water immersion because we do not have access to



Figure 1. Punctate urticaria, facial and ear swelling immediately after exercise challenge in April 2007.

hot water baths in our hospital and the water would wash away the sweat for collection. Given the patient's ChU severity, she was unable or unwilling to exercise sufficiently long to develop a sweat despite two additional attempts. Therefore, alternatives for sweat collection were considered.

Pilocarpine iontophoresis (PI) is the most common diagnostic technique for cystic fibrosis. Although never attempted, for our purpose of ASwST by literature search, we performed PI for sweat collection as described elsewhere.⁶ Briefly, the arm is first cleaned with sterile water. Then pilocarpine 0.5% and an inert electrolyte solution in agar gel discs (Pilogel discs by Wescor, 459 S. Main ST., Logan, UT 84321) were secured to the patient's arm and connected to a battery-powered stimulator (Macroduct sweat collection system, Model 3700-SYS; Wescor, Logan, UT). The current and time typically necessary to drive adequate pilocarpine nitrate into the skin are 1.5 mA for 5 minutes. The collecting device grossly consists of a sponge funneling into a coiled capillary tube with a small amount of dye to mark the sweat front. This device is placed over the pilocarpine-stimulated area for 30 minutes. Variable amounts of sweat are collected depending on the patient (18–135 mg).⁶ Both the patient and the control (H.F.O.) had sweat collected by this method. Given the small amount of sweat collected in the patient, sweat was diluted with an equal amount of saline to make 0.01 mL and injected unfiltered. The control provided more than enough sweat by pilocarpine method and was similarly tested with autologous undiluted, unfiltered sweat. As originally described, a wheal $\geq 9 \times 9$ mm and erythema $\geq 20 \times 20$ mm was interpreted as positive at 15 minutes.⁷ The patient had a positive ASwST intradermal (ID) at 12×12 -mm wheal and 55×60 flare with a negative saline ID (0×0 -mm wheal and flare) and positive histamine control ID of 11×12 -mm wheal and 27×22 flare (Fig. 2). This supported the clinical impression of severe ChU. The control had negative results to ASwST as previously defined with appropriate negative saline and positive histamine controls. On a subsequent day, the control



Figure 2. Findings of sweat collection by pilocarpine iontophoresis and autologous sweat skin testing on patient.

had an identically negative ASwST on sweat gathered after exercise.

Further Clinical Course

Once a positive ASwST was indicated, suggesting anti-sweat-specific IgE, a trial of omalizumab, 300 mg, monthly was instituted according to dosing guidelines based on weight and total IgE (Genentech Novartis, South San Francisco, CA). A validated CU quality of life questionnaire (CU-Q₂OL) was used to subjectively monitor the patient's response to treatment.⁸ Before her second injection, she reported that her severity by CU-Q₂OL had been reduced 50%, from baseline of 97/115 points to 43/115, and has remained reduced (Fig. 3 A). Her ability to exercise without significant urticaria increased over 800%, from <5 minutes to just >40 minutes (Fig. 3 B). She had self-weaned her medications down from eight pills daily to once-daily cetirizine (Fig. 3 C).

DISCUSSION

ChU, first described in 1924, is characterized by unique clinical features: pinpoint-sized, highly pruritic wheals with surrounding erythema that occur after sweating during exercise, strong emotions, hot baths, eating hot or spicy foods, or raising the body temper-

ature.⁹ ChU is believed to account for ~5% of all CU and 30% of all physical urticaria. ChU patients predictably record the greatest disability by QOL scores and are the only urticarial group relatively restricted in sexual activities.¹⁰ ChU typically has its onset during the second or third decade.^{1,3} Overall, prognosis is generally favorable, because 31% of patients have persistence of symptoms ≥ 10 years with an average duration of 7.5 years (range, 3–16 years).^{3,11}

Although classic ChU lesions associated with typical triggers are often enough to suggest the diagnosis, confirmatory testing can be performed. Classically, an ID injection of 0.01 mg of methacholine in 0.1 mL of saline produces a local area of hives and is diagnostic of ChU. However, because only ~1/3 of ChU patients show a positive test, it can not be used to “rule out” ChU and has fallen out of favor.^{3,5} Other specific provocative challenges may include exercise or hot water bath challenge.^{4,5} For hot bath testing, a patient should be submerged partially in a hot water bath at 40–44°C until the core body temperature has increased $\geq 0.7^\circ\text{C}$.^{5,12} Under these conditions, the appearance of generalized urticaria confirms the diagnosis of ChU.⁵

The pathogenesis of ChU is unclear but is generally believed to involve an abnormal cutaneous response in the presence of cholinergic agents,⁴ although certainly

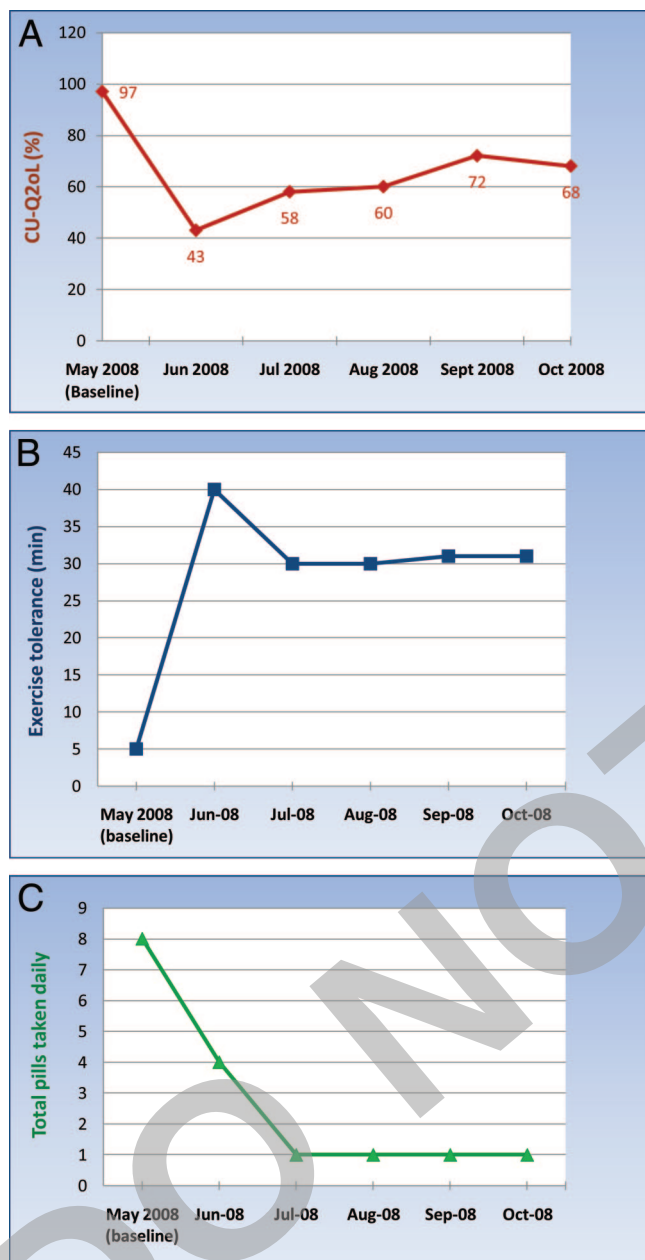


Figure 3. (A) Chronic urticaria quality of life (CU-Q₂OL) scores starting at baseline (worst possible severity is 115 points and best is 0) before her first injection. Subsequent CU-Q₂OL scores obtained at monthly omalizumab injection visits. Patient filled out the CU-Q₂OL questionnaire and reviewed exercise tolerance and the number of pills taken daily for each injection visit. (B) Self-reported exercise tolerance times. Initially, could not exercise >5 minutes before having to stop because of severe urticaria. (C) Number of pills needed for control of cholinergic urticaria. Initially, eight pills were needed and control still was not achieved.

other mediators could be involved. In patients with ChU, injection of acetylcholine into normal appearing skin produces a wheal and flare reaction, often surrounded by smaller satellite lesions.⁵ Adachi and colleagues reported a group of 20 ChU patients who

showed a positive ASwST as well as positive Prausnitz-Kustner tests in all 6 patients in whom the procedure was performed, compared with negative ASwST in 20 control patients.⁷ They used 0.02 mL of various dilutions of sweat, and a positive response was read at 15 minutes and defined as a wheal of >9 × 9 mm or erythema of >20 × 20 mm. The large cutoff in size is caused by irritant effects of sweat.⁷ Although a positive response to autologous skin testing does not prove or disprove the presence of antibodies, it does show histamine-releasing properties of the serum or sweat.¹³ Fukunaga *et al.* showed that there may be two subgroups of ChU patients, a nonfollicular group that shows a positive ASwST and negative ASST, and a follicular ChU group that shows a weak ASwST and positive ASST. They also showed that autologous sweat was able to induce histamine release from basophils, which correlated with the size of the positive ASwST, implying the sweat itself contains factors that can induce histamine release.¹⁴ Adachi *et al.* collected sweat as described by Boysen *et al.*,¹⁵ who described an anaerobic method of collecting large volumes of sweat with less epidermal contamination. They heated the area with a hair dryer and constructed a sweat collector out of petroleum jelly and paraffin oil covered by polyethylene film attached to rubber tubing and a syringe.¹⁵ Otherwise, published articles on the methods of ChU and sweat collection are lacking in further details.^{14,16} Therefore, this is the first study using PI for sweat collection to perform ASwST.

Management of ChU involves avoidance of triggers. Medical therapy is predominantly oral antihistamines, either H₁- and/or H₂-blockers, often at higher doses. Hydroxyzine has been reported to be the drug of choice.^{1,17} Leukotriene inhibitors are often added to standard regimens. Oral anticholinergic agents have not shown efficacy.¹ Danazol has shown effectiveness although its potential for adverse effects limits it to severe cases.¹⁸ Cautious use of β -blocker therapy has been recommended for certain cases because of its anxiolytic effects.¹⁷ Tanaka and colleagues report the successful treatment of a ChU patient with partially purified sweat antigen immunotherapy.¹⁶ Moore-Robinson and Warin described two cases of a successful desensitization regimen in which patients pretreated themselves with antihistamine followed by a hot bath 3 hours later.¹

Although the pathophysiology of ChU still is not known, with the demonstration of a positive immediate skin test response to autologous sweat, we considered omalizumab's anti-IgE mechanism as a viable treatment option. Omalizumab is a recombinant humanized anti-IgE antibody that inhibits the binding of IgE to the high-affinity IgE receptor (Fc ϵ RI) on the surface of mast cells and basophils and reduces the numbers of Fc ϵ RI receptors, thus reducing circulating

levels of free IgE and has been shown to decrease tissue eosinophils, lymphocytes, and IL-4 cells and inhibit early and late-phase responses to allergen.^{19,20} Omalizumab has shown promise in CIU in several recent pilot studies and case reports. In 2007, Spector and Tan reported the rapid improvement of refractory CIU in three patients treated with omalizumab.²¹ In 2008, Kaplan *et al.* reported complete resolution of chronic autoimmune urticaria in 7 of 12 patients treated with omalizumab.²² All of these patients had different serum IgE and anti-IgE receptor antibody profiles and none with ChU. Gober *et al.* reported a successful double-blind, placebo-controlled treatment of CIU with omalizumab without indicating IgE levels or immediate-type hypersensitivity to serum.²³ Metz *et al.* reported the first successful case of omalizumab used to treat ChU, similarly without noting the total IgE level or demonstrating a positive ASST or ASwST.²⁴ Thus, our case is the second reported use of omalizumab in ChU, and the first involving a documented positive ASwST using a novel collection method. Improvement with anti-IgE antibody (omalizumab) suggests a role for IgE in ChU.

CONCLUSIONS

In conclusion, this case shows that PI can be used for sweat collection to perform ASwST in patients with severe ChU and reports the successful use of omalizumab for severe ChU. It is important to distinguish this was not a new means of diagnosis. Because this method produces variable amounts of sweat depending on the patient, filtering and using serial dilutions are recommended for ID testing with sufficient quantities.^{1,3,7,22} If the quantity of collected sweat is limited, then one could consider using undiluted, unfiltered sweat with appropriate informed patient consent. A positive ASwST could serve as rationale for clinical use of omalizumab.

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