Ann Allergy Asthma Immunol 114 (2015) 443–446

Contents lists available at ScienceDirect

Challenging Clinical Cases

Ketotifen use in a patient with fire ant hypersensitivity and mast cell activation syndrome

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ARTICLE INFO

Article history:
Received for publication October 31, 2014.
Received in revised form March 10, 2015.
Accepted for publication March 15, 2015.

Introduction

A 43-year-old white woman residing in Texas with a medical history of persistent asthma controlled on 2 inhalations of 230 μg of fluticasone and 21 μg of salmeterol hydrofluoroalkane twice a day and 10 mg of montelukast by mouth once a day and allergic rhinitis on allergen immunotherapy presented to an allergy and immunology clinic with a history of a systemic reaction thought to be secondary to a wood ant (*Formica rufa*) bite. Immediately after enduring the ant bite, the patient noted erythema, pruritus, and swelling at the bite site. The symptoms rapidly progressed to shortness of breath and wheezing. Diphenhydramine alleviated her large local reaction and her albuterol metered dose inhaler resolved her respiratory symptoms. She also noted that occasionally she experienced a non-triggered flushing sensation and cheek erythema not associated with insect bites.

Although there has been 1 reported case of an anaphylactic reaction to wood ant,[1] it is far less common than hypersensitivity reactions to imported fire ant (IFA). There is no commercially available *F rufa* whole-body or venom extract to assess for wood ant hypersensitivity. Furthermore, IFA hypersensitivity is a significant cause of insect venom-induced anaphylaxis in the southeastern region of the United States and is endemic in the area in which the patient resides.[2,3] Given the rarity of hypersensitivity reactions to wood ants in the literature and the prevalence of IFA and IFA hypersensitivity in the region where the patient resides, the authors assessed for IFA hypersensitivity by checking a specific IFA IgE.

A subsequent laboratory evaluation completed by her allergist showed an elevated IFA (*Solenopsis invicta*) IgE of 1.16 kU/L (positive ≥0.35 kU/L). Given her history of stinging insect hypersensitivity, her baseline serum tryptase level was checked and was elevated at 13.8 μg/L (normal range 0.4–10.9 μg/L).

Owing to her elevated specific IFA IgE and history of systemic reaction to an ant bite, the patient was started on IFA immunotherapy. The patient was treated with an antihistamine before receiving immunotherapy. Patients with a history of IFA hypersensitivity benefit from conventional IFA whole-body extract (IFA-WBE) immunotherapy.[4]

After her first injection of IFA-WBE (0.05 mL, 1:100,000 weight/volume [w/v]), she had an anaphylactic reaction resulting in hypotension, diaphoresis, tachycardia, hypoxia, dizziness, and nausea without shortness of breath, sensation of throat closure, and hives (blood pressure 60/40 mmHg, O_2 saturation 92% on room air, heart rate 124 beats/min and regular). She was immediately treated with an epinephrine auto-injector, intravenous (IV) fluids, IV diphenhydramine, and IV methylprednisolone. She continued to have these symptoms; then she was treated and stabilized with a second epinephrine auto-injector and sent to a local emergency department with an emergency medical service. At that time, all allergen and IFA-WBE immunotherapy was stopped.

The patient's anaphylactic reaction to a relatively low concentration of IFA-WBE immunotherapy, her history of non-triggered flushing sensations and cheek erythema, and elevated baseline serum tryptase level raised concern for a mast cell disorder. Patients with mast cell activation syndrome (MCAS) have episodic non-triggered symptoms consistent with mast cell mediator release that improves with anti-mediator therapy such as H_1 and H_2 antihistamines.[5] H_1 and H_2 histamine receptors are G-protein–coupled receptors that are in equilibrium between active and inactive states. Histamine acts as a receptor agonist that shifts the equilibrium of the receptor to the active state, inducing signaling pathways that lead to bronchoconstriction, vasodilation, and smooth muscle relaxation. H_1 and H_2 antihistamines serve as inverse agonists that shift the equilibrium of the receptor to the inactive state, thus preventing the symptoms caused by mast cell mediator release in patients with MCAS.[6] One study has shown that patients with systemic mastocytosis, a mast cell disorder, are at increased risk of having anaphylaxis, especially in the setting of hymenoptera exposure.[7] Patients with MCAS are at increased risk of having anaphylactic symptoms from mast cell mediator release.

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Disclosure: Authors have nothing to disclose.

http://dx.doi.org/10.1016/j.anai.2015.03.009

Table 1
Imported fire ant desensitization protocol

Amount of IFA-WBE (mL)	Concentration of IFA-WBE
Day 1	
0.1 mL	1:10,000,000
0.3 mL	
0.5 mL	
0.1 mL	1:1,000,000
0.2 mL[a]	
0.3 mL	
0.4 mL	
0.5 mL	
0.1 mL[b]	1:100,000
0.2 mL	
0.3 mL	
0.4 mL	
0.5 mL	
0.1 mL	1:10,000
0.2 mL	
0.3 mL	
0.4 mL	
Day 2	
0.4 mL	1:10,000
0.5 mL	
0.1 mL	1:1,000
0.2 mL[c]	
0.3 mL	
0.4 mL	
0.5 mL	
0.1 mL	1:100
0.2 mL	
0.3 mL	
Day 8	
0.4 mL	1:100
Day 15	
0.5 mL	1:100
Day 22	
0.5 mL	1:100

Abbreviation: IFA-WBE, imported fire ant whole-body extract (doses were given at 30-minute intervals).
[a]Ten minutes after the dose was given, the patient experienced facial erythema and pruritus that resolved without treatment. The last tolerated dose was repeated and the protocol was continued.
[b]Fifteen minutes after the dose was given, the patient had an anaphylactic reaction; the protocol was suspended and resumed at 0.1 mL of the 1:1,000,000 concentration the following day.
[c]Eighteen minutes after the dose was given, the patient experienced facial erythema and discomfort. The patient was treated once with 25 mg of diphenhydramine intravenously. Symptoms resolved after treatment. The last tolerated dose was repeated and the protocol was continued.

A new elevated baseline serum tryptase level was evaluated with a repeat baseline serum tryptase level (12.9 μg/L, normal range 0.4–10.9 μg/L) and 24-hour urine histamine and prostaglandin D_2. Urine histamine was within normal range, but urine prostaglandin D_2 was elevated at 436 ng per 24 hours (normal range 100–280 ng per 24 hours). Bone marrow biopsy did not demonstrate any diagnostic morphologic or immunophenotypic evidence of mast cell disease (mastocytosis). The patient was diagnosed with MCAS and treated with 180 mg of fexofenadine by mouth every 12 hours and with 150 mg of ranitidine by mouth every 12 hours. She explained that as long as she maintains this antihistamine regimen, she does not have flushing episodes with cheek erythema. A few months after the bone marrow biopsy, the patient's persistent asthma was controlled on 2 inhalations of 230 μg of fluticasone and 21 μg of salmeterol hydrofluoroalkane twice a day and 10 mg of montelukast by mouth once a day but then became uncontrolled. Based on the serum total IgE of 117 IU/mL (normal range 0–380 IU/mL), the patient was started on 225 mg of omalizumab subcutaneously every 2 weeks. In addition, she was started on an inhaler with 18 μg of tiotropium once a day. The patient was on omalizumab and tiotropium for approximately 5 months before being referred to the authors' clinic.

Table 2
Pre- and post-medications for IFA-WBE IT

Night before IFA-WBE IT	Morning of IFA-WBE IT	Evening of IFA-WBE IT
fexofenadine 180 mg po prednisone 20 mg po ketotifen 2 mg po montelukast 10 mg po	fexofenadine 180 mg po ketotifen 2 mg po diphenhydramine 25 mg po	ketotifen 2 mg po

Abbreviations: IFA-WBE IT, imported fire ant whole-body extract immunotherapy; po, per oral.

Studies have shown that patients with a history of IFA venom anaphylaxis benefit from a rush IFA-WBE immunotherapy protocol.[8–11] Furthermore, at least 1 study has shown that omalizumab can lower the risk of anaphylactic reactions induced by rush immunotherapy.[12] In their literature search, the authors did not find a protocol devised for a patient with IFA hypersensitivity with MCAS. Therefore, they used a modified version of the Wilford-Hall IFA-WBE 2-day rush protocol.[8] Given her high risk of mortality from IFA venom, history of IFA-WBE immunotherapy-induced anaphylaxis, and MCAS, the authors administered the immunotherapy protocol in an intensive care setting and monitored her respiratory status with frequent bedside spirometry. The protocol is presented in Table 1. All doses were given at 30-minute intervals. Spirometry was stable and remained at baseline throughout the protocol. The combination of pre- and post-medications used in the protocol is listed in Table 2.

Within 15 minutes of the 0.1-mL 1:100,000 w/v IFA-WBE injection on day 1 of the rush IFA-WBE immunotherapy protocol, the patient had an anaphylactic reaction with symptoms including hoarse voice, sensation of throat closure, flushing, tachycardia, and shortness of breath. Her blood pressure and O_2 saturations remained stable. Her heart rate was 128 beats/min and regular. She was given an auto-injector with 0.3 mg of epinephrine injected intramuscularly into the right thigh and 50 mg of IV diphenhydramine. The patient continued to have increasing shortness of breath and sensation of throat closure. She was given another auto-injector with 0.3 mg of epinephrine injected intramuscularly into the left thigh. She noticed a dramatic improvement after the second epinephrine injection. She was given nebulized albuterol and 60 mg of IV methylprednisolone. Ten minutes after the second epinephrine injection, her symptoms had completely resolved. At that time, her vital signs and physical examination findings returned to baseline levels. The rush IFA-WBE protocol was suspended at that time.

After discussing the risks and benefits of continuing or stopping the immunotherapy protocol, the patient decided to resume the rush IFA-WBE protocol the following day. Although she had a history of hypersensitivity reaction to an ant bite and a modestly elevated IFA-specific serum IgE, the authors believed the 2 anaphylactic episodes that occurred with extremely low doses of IFA-WBE immunotherapy were related to a large extent to her underlying MCAS. For this reason ketotifen, a mast cell stabilizer, was added to her pre- and post-immunotherapy mediation regimen (Table 2).

Ten minutes after the 0.2-mL 1:1,000,000 w/v IFA-WBE injection on day 2 of the rush immunotherapy protocol, the patient complained of pruritus and erythema in her left cheek that resolved within 20 minutes without rescue medications. She denied any shortness of breath, chest tightness, sensation of throat closure, dizziness, rhinitis symptoms, wheezing, hoarse voice, or nausea. Eighteen minutes after the 0.2-mL 1:1000 w/v IFA-WBE injection on day 3 of the rush immunotherapy protocol, the patient noted a burning sensation and erythema in both cheeks and a flushed sensation. The symptoms resolved within 10 minutes of receiving 25 mg of IV diphenhydramine. She denied any shortness of breath,