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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 $\mu\text{g/L}$ (normal range 0.4–10.9 $\mu\text{g/L}$).

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, O₂ 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 H₁ and H₂ antihistamines.⁵ H₁ and H₂ 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. H₁ and H₂ 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>

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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	
0.2 mL ^a	1:1,000,000
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	1:10,000
0.1 mL	
0.2 mL	
0.3 mL	
0.4 mL	1:100,000
0.5 mL	
0.1 mL	
0.2 mL	
0.3 mL	1:100
0.4 mL	
0.5 mL	
0.1 mL	
Day 2	
0.4 mL	1:10,000
0.5 mL	
0.1 mL	
0.2 mL ^c	
0.3 mL	1:1,000
0.4 mL	
0.5 mL	
0.1 mL	
0.2 mL	1:100
0.3 mL	
0.4 mL	
0.5 mL	
Day 8	
0.4 mL	1:100
0.5 mL	
0.1 mL	
0.2 mL	
Day 15	
0.5 mL	1:100
0.1 mL	
0.2 mL	
0.3 mL	
Day 22	
0.5 mL	1:100
0.1 mL	
0.2 mL	
0.3 mL	

Abbreviation: IFA-WBE, imported fire ant whole-body extract (doses were given at 30-minute intervals).

^aTen 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.

^bFifteen 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.

^cEighteen 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 $\mu\text{g/L}$, normal range 0.4–10.9 $\mu\text{g/L}$) 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 medication 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,

chest tightness, sensation of throat closure, dizziness, rhinitis symptoms, wheezing, hoarse voice, or nausea. Subsequently she completed the rush IFA-WBE protocol in the intensive care unit without adverse reaction. The remaining injections beginning on day 8 were done in a clinic attached to a hospital. The patient tolerated the 0.4-mL 1:100 w/v IFA-WBE injection on day 8 and the 0.5-mL 1:100 w/v IFA-WBE injection on day 15 without adverse effects. Fifteen minutes after the 0.5-mL 1:100 w/v injection on day 22, the patient noted itching at the injection site. A dime-size wheal with a quarter-size flare was noted at the site. The patient denied shortness of breath, throat tightness, diffuse pruritus, or hives. She was treated with 25 mg of diphenhydramine by mouth. Symptoms resolved within 1 hour.

The patient had successfully completed the rush IFA-WBE IT protocol and reached maintenance with the use of several pre- and post-medications including oral ketotifen.

Discussion

The authors have presented a case of a patient with MCAS and IFA venom hypersensitivity. The reported anaphylactic reaction to the ant bite could have been secondary to direct mast cell activation from MCAS or specific IgE-mediated hypersensitivity. The likelihood of a direct mast cell activation mechanism is decreased by the fact that the patient has not had adverse reactions to other insect stings and has tolerated maintenance doses of aeroallergen immunotherapy for more than 6 months without anaphylaxis. Furthermore, based on her elevated specific IgE to IFA venom and history of ant bite- and IFA-WBE immunotherapy-induced anaphylaxis, the authors believed this patient had an IgE-mediated hypersensitivity to IFA venom requiring IFA-WBE immunotherapy. The patient did tolerate rush IFA-WBE immunotherapy despite being on pre-medications that included antihistamines, anti-leukotriene, steroid, and omalizumab. Given her history of MCAS, the authors hypothesized that ketotifen, a mast cell stabilizer, would allow her to tolerate IFA-WBE immunotherapy.

Mast cells are derived from hematopoietic stem cells and differentiate in the tissues. They are found in numerous areas of the body and are prevalent on mucosal and endothelial surfaces that are exposed to the external environment. IgE-mediated and IgE-independent mechanisms activate and result in degranulation of mast cells. Degranulated mast cells release mediators, including histamine, heparin, and proteases, synthesize arachidonic acid metabolites from lipid membranes, and secrete cytokines and chemokines. Mastocytosis is a mast cell disease caused by abnormal proliferation of mast cells. Without mast cell proliferation, mast cell disorders can exist in states where mast cells activate at a lower stimulation threshold. Monoclonal MCAS, like systemic mastocytosis, is characterized by the presence of at least 1 marker of clonality, including c-KIT D816V point mutation, other c-KIT mutations, or aberrant CD25 marker on bone marrow analysis. However, unlike systemic mastocytosis, monoclonal MCAS will not present with multifocal mast cell aggregates in the bone marrow. MCAS, like monoclonal MCAS, will present with mediator release symptoms, a response to anti-mediator therapy, and normal to mildly increased baseline tryptase level. However, MCAS will not have point mutations or aberrant markers on bone marrow mast cell analysis.^{5,13}

The most frequent cause of insect venom hypersensitivity in the southeastern region of the United States is IFA.² IFA stings can cause significant large local reactions leading to secondary infections and systemic anaphylactic reactions that are potentially fatal. Despite measures to avoid IFA stings, patients do not have a decreased frequency of stings.¹¹ Therefore, IFAs present a significant health hazard in endemic regions. IFA immunotherapy can decrease the risk of subsequent systemic hypersensitivity reactions.³ A retrospective study showed that patients with a history of anaphylaxis

to IFA treated with WBE conventional immunotherapy had a significant decrease in reaction rates to field stings compared with patients with a history of IFA-induced anaphylaxis not treated with immunotherapy.⁴ Conventional immunotherapy schedules can require up to 6 months to reach maintenance, leaving patients with a history of IFA-induced anaphylaxis at risk of fatal reactions during the prolonged buildup period.⁹ Several studies have demonstrated the safety and efficacy of 1- and 2-day rush IFA-WBE immunotherapy protocols with and without pre-medications; however, none of the patients studied had a mast cell activation disorder.^{8–10}

One study has demonstrated that omalizumab decreases the risk of anaphylaxis induced by rush immunotherapy in patients with ragweed allergic rhinitis 5-fold compared with rush immunotherapy alone. Furthermore, immunotherapy has been shown to be more effective in patients treated concomitantly with omalizumab compared with immunotherapy alone based on symptom severity scores during ragweed season.¹² Another study has demonstrated that omalizumab used with specific immunotherapy for patients with seasonal allergic rhinitis and seasonal allergic asthma is safe and effective in decreasing symptom load compared with specific immunotherapy alone.¹⁴

The present patient was diagnosed with MCAS based on episodic symptoms consistent with mast cell mediator release, including flushing and wheezing, response of these symptoms to treatment with H₁ antihistamines and H₂ blockers, mildly elevated baseline tryptase, elevated 24-hour urine prostaglandin D₂ level, and lack of morphologic or immunophenotypic evidence of mast cell disease on bone marrow analysis. In addition, she had an anaphylactic reaction from a suspected wood ant bite and documented elevation in IFA-specific serum IgE. With her previous allergist, she was noted to have an anaphylactic reaction from IFA-WBE immunotherapy at the 0.05-mL 1:100,000 w/v dose. Given her history of MCAS, persistent asthma, IFA hypersensitivity, and anaphylaxis to IFA-WBE immunotherapy, a modified version of the Wilford-Hall 2-day rush IFA-WBE immunotherapy protocol was used in the intensive care setting using pre-medications that included omalizumab. The patient received 225 mg of omalizumab subcutaneously every 2 weeks for 6 months before starting IFA-WBE rush immunotherapy. Despite pretreatment with anti-leukotriene, steroids, antihistamines, and omalizumab, the patient had anaphylaxis at the 0.1-mL 1:100,000 w/v dose of IFA-WBE immunotherapy on day 1 of the protocol.

Given the patient's history of MCAS, the authors hypothesized that a mast cell stabilizer could be effective in preventing anaphylactic episodes induced by IFA-WBE immunotherapy. Ketotifen inhibits the release and/or activity of mast cell mediators, including histamine, arachidonic acid metabolites, and leukotrienes.¹⁵ Before resuming the protocol on day 2, the patient was started on 2 mg of ketotifen by mouth the night before, 2 mg by mouth the morning of, and 2 mg by mouth the evening of IFA-WBE immunotherapy. Except for 2 episodes of cheek erythema and pruritus, the patient tolerated the remainder of the modified rush protocol. She successfully reached maintenance IFA-WBE immunotherapy in the outpatient setting using the pre- and post-medications listed in Table 2.

In conclusion, the authors have presented a case of a 43-year-old white woman with MCAS, persistent asthma, allergic rhinitis, and IFA allergy who experienced IFA-WBE immunotherapy-induced anaphylaxis during the buildup phase of the 2-day rush protocol despite being on omalizumab. Given her history of MCAS, the authors hypothesized that ketotifen, which has mast cell stabilizing effects, would prevent subsequent IFA-WBE immunotherapy-induced anaphylactic reactions. Based on the results of this case, the authors suggest that oral ketotifen should be considered a prophylactic therapy in patients with mast cell disorders undergoing venom immunotherapy.

References

- [1] Klotz JH, deShazo RD, Pinnaas JL. Adverse reaction to ants other than imported fire ants. *Ann Allergy Asthma Immunol*. 2005;95:418–425.
- [2] Freeman TM. Hymenoptera hypersensitivity in imported fire ant endemic area. *Ann Allergy Asthma Immunol*. 1997;78:369–372.
- [3] Stafford CT. Hypersensitivity to fire ant venom. *Ann Allergy Asthma Immunol*. 1996;77:87–99.
- [4] Freeman TM, Hylander R, Ortiz A, et al. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol*. 1992;90:210–214.
- [5] Akin C, Valent P, Metcalfe DD, et al. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol*. 2010;126:1099–1104.
- [6] Harvey RA, Pamela CC. *Pharmacology*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2006.
- [7] Gulen T, Hagglund H, Dahlen B, et al. High prevalence of anaphylaxis in patients with systemic mastocytosis—a single-centre experience. *Clin Exp Allergy*. 2014;44:121–129.
- [8] Tankersley MS, Walker RL, Butler WK, et al. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. *J Allergy Clin Immunol*. 2002;109:556–562.
- [9] Judd CA, Parker AL, Meier EA, et al. Successful administration of a 1-day imported fire ant rush immunotherapy protocol. *Ann Allergy Asthma Immunol*. 2008;101:311–315.
- [10] Arseneau AM, Nesselroad TD, Dietrich JJ, et al. A 1-day imported fire ant rush immunotherapy schedule with and without premedication. *Ann Allergy Asthma Immunol*. 2013;222:562–566.
- [11] Letz AG, Quinn JM. Frequency of imported fire ant stings in patients receiving immunotherapy. *Ann Allergy Asthma Immunol*. 2009;102:303–307.
- [12] Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2006;117:134–140.
- [13] Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012;157:215–225.
- [14] Kopp MV, Hamelmann E, Zielen S, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy*. 2009;39:271–279.
- [15] Sokol KC, Amar NK, Starkey J, Grant JA. Ketotifen in the management of chronic urticaria: resurrection of an old drug. *Ann Allergy Asthma Immunol*. 2013;111:433–436.