Anaphylaxis After Hymenoptera Sting: Is It Venom Allergy, a Clonal Disorder, or Both?

Mariana C. Castells, MD, PhD, Jason L. Hornick, MD, PhD, and Cem Akin, MD, PhD *Boston, Mass*

A 47-year-old man presented with loss of consciousness 5 minutes after being stung by a yellow jacket in his backyard. Epinephrine and fluids were required for resuscitation. Allergy evaluation revealed specific IgE to yellow jacket and honeybee, and the patient was started on venom immunotherapy. He had systemic reactions during buildup and a severe anaphylactic episode requiring 3 doses of intramuscular epinephrine at maintenance doses. Immunotherapy was discontinued. Serum tryptase level after 1 such episode was 29 ng/mL, with a baseline level of 25 ng/mL 4 weeks later. The physical examination was unremarkable including no skin lesions of cutaneous mastocytosis. Because of elevated baseline tryptase level, a bone marrow biopsy was performed, which revealed multifocal dense infiltrates of mast cells. A diagnosis of systemic mastocytosis was made. The patient was treated with omalizumab and was able to tolerate immunotherapy and is currently maintained on lifelong immunotherapy. He was restung in the field and has not had anaphylaxis. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:350-5)**

Key words: *Mast cells; Hymenoptera; c-kit mutations; Mastocytosis*

The presentation, diagnosis, and molecular features of a subset of indolent systemic mastocytosis (ISM) associated with hymenoptera anaphylaxis are reviewed, and the approach to management and treatment is discussed. Patients with anaphylactic reactions to hymenoptera venom presenting with hypotension are at an increased risk for having systemic mastocytosis as the underlying diagnosis, modifying the severity of the presentation. A baseline serum tryptase level is recommended as a screening test for all patients with hymenoptera anaphylaxis. A bone marrow biopsy and aspiration should be considered for those with elevated baseline tryptase levels. Complications of systemic mastocytosis include osteopenia and osteoporosis, which can lead to bone fractures and can be prevented with early treatment. Progression to aggressive mastocytosis or an associated hematological malignancy can occur in a small subset of patients with systemic mastocytosis but has not been documented in patients presenting initially with hymenoptera anaphylaxis. A small number of patients can also have severe anaphylactic reactions to certain drugs (including nonsteroidal anti-inflammatory drugs, opioids, vancomycin, and muscle relaxants) and contrast dyes. Premedication regimens similar to those used in prophylaxis of contrast dye allergy have been proposed before medical procedures involving general anesthesia, although the efficacy of these regimens has not been systemically evaluated. Upper gastrointestinal irritation due to gastric acid hypersecretion is another common complication and can be prevented by the use of H2 antihistamines and proton pump inhibitors.

CLINICAL PRESENTATION

A 47-year-old man working in his backyard was stung by a yellow jacket. He felt weak and dizzy with tunnel vision and lost consciousness within 5 minutes. Epinephrine was injected intramuscularly in the field, and he was brought to the emergency room. He received fluids, antihistamines, and glucocorticosteroids, and he recovered without sequelae. Evaluation by skin testing 6 weeks later was negative for all hymenoptera venoms, possibly due to the anergic period following anaphylaxis, but specific IgE was positive for yellow jacket (class II) and honeybee (class I). He was started on venom immunotherapy (VIT) with mixed vespids and honeybee at an outside allergy clinic. He had mild to moderate systemic reactions while receiving buildup doses, requiring several epinephrine injections, but was able to reach maintenance and started a program of 300 μg of mixed vespids and 100 μg of honeybee every 4 weeks. At the second injection of maintenance, he was 2 weeks late (6 weeks since his last injection) and had immediate tunnel vision, hypotension, oxygen desaturation, and loss of consciousness and required 3 doses of intramuscular epinephrine for resuscitation. A tryptase level (the exact timing was unclear but within 24 hours of the reaction) was found to be elevated at 29 ng/mL. Immunotherapy was discontinued, and the patient care was transferred to the Brigham and Women's Hospital Mastocytosis Center. A tryptase baseline repeat level 4 weeks later was 25 ng/mL. The patient had a full-body skin examination that ruled out urticaria pigmentosa, mastocytoma, or other forms of cutaneous mastocytosis that could explain the elevation in the tryptase level. He had no organomegaly or lymphadenopathy. The patient had a history of allergic rhinitis

Mastocytosis Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

Conflicts of interest: M. C. Castells is on the American Academy of Allergy, Asthma & Immunology Board; has received consultancy fees from Sanofi; is employed by Brigham and Women's Hospital; has received research support from Ovations for the Cure; has received lecture fees from the Kansas Allergy Society; and receives royalties from UpToDate. C. Akin has received consultancy fees from Novartis, Patara Pharma, and Blueprint Medicines; is employed by Brigham and Women's Hospital; and has a patent through the National Institutes of Health (LAD2 cell line). J. L. Hornick declares that he has no relevant conflicts of interest.

Received for publication January 26, 2015; revised March 28, 2015; accepted for publication March 30, 2015.

Available online April 7, 2015.

Corresponding author: Mariana C. Castells, MD, PhD, Harvard Medical School, Brigham and Women's Hospital, 1 Jimmy Fund Way, Smith Bldg, Rm 626D, Boston, MA 02115. E-mail: mcastells@partners.org.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.03.015

Abbreviations used
MMAS- Monoclonal mast cell activation syndrome
VIT- Venom immunotherapy

and mild asthma and used over-the-counter antihistamines and bronchodilators intermittently. His review of systems was positive for frequent episodes of flushing associated with palpitations, abdominal bloating and pain, and intermittent diarrhea for the last 2 to 3 years. He complained of generalized bone pain and mild depression and anxiety. He denied food allergies and had not used oral steroids or been hospitalized for his asthma. A bone marrow biopsy was performed because of the baseline elevated tryptase level and showed small perivascular aggregates of mast cells including atypical spindle-shaped forms, which were positive for CD25 (Figure 1). The patient received a diagnosis of ISM. His bone marrow did not show evidence of myelodysplastic or myeloproliferative disorders, and his peripheral blood cell counts were within normal range without eosinophilia. His liver enzymes and metabolic panel were normal, and a bone densitometry was normal without evidence of osteopenia or osteoporosis. Treatment with omalizumab 300 mg every 4 weeks was initiated and immunotherapy restarted for mixed vespids and honeybee 2 weeks after the second injection of omalizumab. The patient tolerated omalizumab and immunotherapy without complications and reached maintenance doses. Omalizumab was discontinued after 6 months of maintenance immunotherapy. The patient has been maintained on immunotherapy without omalizumab for 24 months and has not presented any further anaphylactic events. He has been restung in the field once with associated mild flushing and dizziness responding to oral antihistamines, but no changes in vital signs and he did not require epinephrine.

ELEVATED TRYPTASE LEVEL AS A RISK FACTOR FOR HYMENOPTERA ANAPHYLAXIS

Tryptase is the major protease produced by mast cells. It is produced in a protryptase form and cleaved to form mature and enzymatically active tryptase. Mature tryptase is stored in mast cell granules, whereas protryptase is constitutively secreted. Levels of mature (and total) tryptase in serum peak in about 1 hour after a systemic allergic reaction and return to baseline after 4 hours. Elevated baseline tryptase levels raise suspicion for states of increased mast cell burden such as mastocytosis.[1]

The prevalence of anaphylaxis to hymenoptera stings appears to be around 3% in the adult US population.[2] The level of specific IgE detectable by blood or skin testing does not predict the severity of symptoms of the reaction.[3] Because tryptase level has been elevated during severe hymenoptera reactions and at baseline in some of the patients, an associated mast cell disorder that could explain the severity and pattern of anaphylaxis has been recently investigated. Mastocytosis is a disorder characterized by the abnormal proliferation and accumulation of clonal mast cells in tissues, harboring the *KIT* D816V mutation and showing aberrant CD25 expression, generally accompanied by elevated baseline tryptase levels.[4] Classification of mastocytosis recognizes ISM as the most common form, which can present with tryptase levels below 20 ng/mL and in the absence of skin lesions.[5] Ludolph-Hauser et al[6] reported that patients with elevated baseline tryptase levels of greater than 13.5 ng/mL, and hence an increased burden of total body mast cells, were more likely to experience severe reactions than did those with normal tryptase levels. Almost all patients with elevated tryptase levels in that study were found to have skin manifestations of mastocytosis (urticaria pigmentosa or telangiectasia macularis eruptiva perstans) on careful inspection of the skin. Akin et al[7] and Sonneck et al[8] reported 2 patients with a history of hymenoptera anaphylaxis who had normal tryptase levels and no cutaneous findings of mastocytosis but had abnormal clonal mast cells expressing the aberrant surface marker CD25 and carrying the *KIT* D816V mutation. Interestingly, these patients did not meet the full criteria to be diagnosed with systemic mastocytosis, and therefore were termed to have "monoclonal mast cell activation syndrome" (MMAS).[7,8]

A large multicenter European study aiming to determine the factors associated with hymenoptera reaction severity examined 962 patients who had systemic reactions.[9] Elevated baseline tryptase levels, along with angiotensin-converting enzyme inhibitor therapy, male sex, vespid sting, and a history of milder reactions, were identified as determinants of the severity of reactions. Systemic reactions to honeybees are also recognized to be a risk factor.[3] Bonadonna et al[10] reported the largest single-center series to evaluate clonal mast cells in hymenoptera anaphylaxis. In this series of 379 patients, 11.6% had elevated tryptase levels, defined as greater than 11.4 ng/mL. These patients were evaluated with bone marrow biopsies to look for evidence of mast cell disease; 65% had evidence of either mastocytosis or MMAS. Interestingly, when a cohort of 329 patients with systemic mastocytosis was analyzed for the presence of venom anaphylaxis, levels of tryptase above the normal range and up to 28 ng/mL were associated with increased risk but higher levels were not associated with increased risk.[11] Elevated baseline tryptase levels have also been recognized as a risk factor for systemic reactions during VIT.[12] Although the patient presented here was late by 2 weeks for his maintenance immunotherapy injection, reactions can occur at any time during the buildup phase or maintenance in patients with mastocytosis.[13]

In summary, the cumulative experience suggests that elevated baseline tryptase levels and the presence of clonal mast cell disease (mastocytosis or MMAS) are strong risk factors determining the severity of hymenoptera reactions. Patients with elevated tryptase levels may or may not have skin lesions of mastocytosis.[14] The bone marrow biopsy may show characteristic mast cell infiltrates of systemic mastocytosis or more limited involvement in the form of MMAS.[15]

Diagnosis of mastocytosis

Mastocytosis is a clonal neoplastic disorder of mast cells and their hematopoietic progenitors that can be broadly categorized into cutaneous and systemic variants. By definition, patients with cutaneous mastocytosis have pathologic mast cell collections limited to the skin, whereas patients with systemic mastocytosis have bone marrow or other extracutaneous involvement proven by biopsy, with or without skin lesions.[16] Cutaneous mastocytosis is the most common diagnosis in infants and children,[17] whereas systemic mastocytosis is generally found in patients diagnosed as an adult. Systemic mastocytosis can be further subdivided into 4 variants on the basis of the presence or absence of tissue dysfunction and other hematologic disorders (Table I).[4,18] The most common category of systemic mastocytosis is ISM, which is associated with a survival rate comparable