

SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

When yellow jackets attack: Recurrent and severe anaphylactic reactions to insect bites and stings

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A 61-year-old male with no significant past medical history was referred for an evaluation of recurrent, provoked anaphylactic reactions to insect stings and bites. Seven years before our evaluation, he experienced an episode of syncope immediately after being stung by several yellow jackets (*Vespula maculifrons*). Although he had been stung before without incident, most recently several years prior, on this occasion he lost and then regained consciousness after an estimated 20 minutes. There was no urticaria, angioedema, shortness of breath, stridor, or seizure activity associated with this episode. One year later, after a nearly identical scenario, the patient was prescribed subcutaneous epinephrine to abort future events.

Insect venom is a common cause of anaphylaxis, and is responsible for 40 deaths annually in the United States [1]. Insects from the order Hymenoptera, which includes yellow jackets, are the most common provacateurs [2]. The fact that this patient had an anaphylactic reaction to a yellow jacket sting is not unusual; up to 3% of the adult population have systemic allergic reactions to insect venom [3]. However, several features of his presentation were atypical. Anaphylaxis usually occurs in patients younger than 20, and a significant number of patients with allergic reactions have a history of atopy [4]. Our patient had never previously experienced an anaphylactic reaction to insect encounters, which serves as the best predictor for the risk of developing future anaphylactic reactions [4]. Finally, the most common symptoms of anaphylaxis are dermal, [4] and this patient had no skin manifestations.

Two years later, the patient was bitten by a triatoma (*Triatoma protracta*), which resulted in a syncopal event lasting 20 minutes. He did not self-administer epinephrine. One year later, the patient was again stung by several yellow jackets. He became lightheaded with blurry vision, but was able to administer the epinephrine, and his symptoms quickly resolved without loss of consciousness. Three years later, after removing a tick (*Rhipicephalus sanguineus*), he had a brief syncopal episode prior to which he was able to administer epinephrine. Finally, several months before his visit to our clinic, he was stung by an estimated two dozen yellow jackets. He administered epinephrine, called emergency services, and was found by the response

personnel to be unconscious and pulseless. After intravenous administration of epinephrine, he quickly recovered, and was discharged from the hospital the next day.

Anaphylactic reactions to triatomas and ticks are uncommon [5,6]. Although typical acquired allergy-mediated anaphylaxis remains in the differential for this patient, other diagnoses must be considered given the unusual and uncommon features of his presentation. The differential diagnosis for syncope with anaphylaxis in the absence of skin findings includes vasovagal syncope or panic attacks, although the severity of his symptoms and their reversal with epinephrine make these unlikely diagnoses. Scombroidosis, resulting from the intake of large amounts of histamine after ingestion of poorly stored fish, can result in anaphylactic symptoms in the absence of urticaria, but is usually also associated with gastrointestinal symptoms such as vomiting or diarrhea. Acute serum sickness, endotoxin-mediated septic shock, and superantigen-mediated toxic shock syndromes are typically associated with fevers, which our patient did not exhibit. Carcinoid syndromes, pheochromocytoma, and acute attacks of hereditary and acquired angioedema caused by C1 esterase inhibitor deficiency can all be associated with syncope without urticaria. However, our patient's symptomatic temporal association with insect exposure would not be readily explained by these diagnoses. The same would apply to more common causes of syncope such as seizures, hypoglycemia or primary cardiac or pulmonary events.

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Mastocytosis, a clinically heterogeneous group of disorders characterized by the abnormal accumulation of clonal mast cells (MCs) in one or more organs, can increase the risk of anaphylaxis to insect bites and stings [7,8]. Disease manifestations range from mild, intermittent skin lesions to an aggressive neoplasm with a poor prognosis. Clinical signs and symptoms, including hypotension, shock, headache, diarrhea, abdominal, bone, and soft tissue pain, are due to organ infiltration resulting in dysfunction as well as the release of mediators after MC activation. The D816V mutation in the gene encoding *KIT* results in constitutive receptor tyrosine kinase activity and is identified in over 80% of patients with systemic mastocytosis (SM) [9].

The World Health Organization (WHO) distinguishes cutaneous mastocytosis, with manifestations limited to the skin, from SM, which requires one major and one minor or three minor criteria to confirm the diagnosis (Table I) [10]. SM is further classified into six distinct variant subtypes: indolent, SM with associated clonal hematological non-mast

cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), mast cell sarcoma, and extracutaneous mastocytoma [10]. It is unusual for patients with ASM to exhibit cutaneous manifestations [11]; patients with more indolent mast cell disease variants more frequently demonstrate these symptoms [12]. However, isolated bone marrow mastocytosis, a subtype of indolent SM, is typically characterized by a lack of skin lesions and a low serum tryptase level [11].

To help further distinguish between a clonal and reactive etiology, allergic skin testing was recommended to determine whether sensitization to insect venom was present.

A workup revealed negative skin tests for antibodies against wasps, bees, hornets, and yellow jackets. Venom-specific IgE tests for honey bee, hornet, and wasp venom were negative; the yellow jacket test was positive. A complete blood count and differential were unremarkable, and a serum tryptase, not sampled at the time of an acute episode, was mildly elevated (12.2 ng/mL, normal = 0.4–10.9 ng/mL). On our examination, the patient had no lesions that were suspicious for cutaneous mastocytosis, no Darier's sign, and no organomegaly.

The absence of a positive skin test for hymenoptera venom suggests that sensitization to these toxins is not the causative factor in this patient's anaphylaxis. The positive serum IgE for yellow jacket venom is an expected finding in patients who have recently been stung. Anaphylaxis from insect stings in the absence of a positive skin test should prompt a workup for SM.

A bone marrow aspirate and biopsy were performed. The aspirate differential revealed 1% mast cells, of which more than 25% were spindle-shaped (Fig. 1A). A trephine bone marrow biopsy revealed a loose collection of mast cells with abundant pale eosinophilic cytoplasm on hematoxylin and eosin staining in a non-paratrabeular location. Mast cells expressed tryptase, CD117, and CD25, and lacked expression of CD2 by immunohistochemistry (IHC), comprising ~5% of total

TABLE I. 2008 World Health Organization Diagnostic Criteria for Systemic Mastocytosis^a

Major criterion
Multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs(s).
Minor criteria
1. In biopsy sections of bone marrow or other extracutaneous organs, $>25\%$ of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or, of all mast cells in bone marrow aspirate smears, $>25\%$ are immature or atypical.
2. Detection of an activating point mutation at codon 816 of <i>KIT</i> in bone marrow, blood or another extracutaneous organ.
3. Mast cells in bone marrow, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
4. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

^a Diagnosis of systemic mastocytosis requires the presence of the major criterion and one minor criterion or at least three minor criteria.

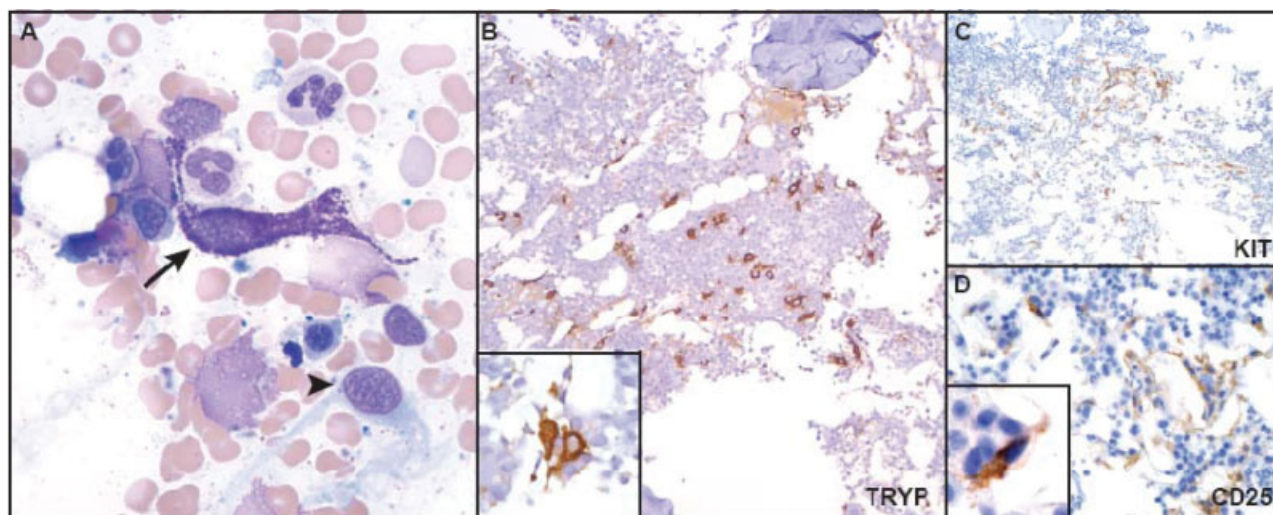


Figure 1. Bone marrow aspirate and biopsy. A: A spindle-shaped mast cell with many granules is shown (arrow), while at lower right a degranulated spindle-shaped cell is present in the aspirate smear (arrowhead), $\times 1,000$ magnification. B: Immunohistochemistry performed on the core biopsy highlights a mild increase in mast cells using an antibody directed against tryptase, $\times 200$ magnification. A loose collection of mast cells is present, with many spindled forms seen at higher magnification (inset, $\times 1,000$). Immunohistochemistry also shows the spindled mast cells express CD117 (C) and CD25 (D), with inset image at $\times 1,000$ magnification showing the spindle-shaped cells.

TABLE II. Reported Cases of Monoclonal Mast Cell Activation Syndrome (MMAS)

Reference (Year)	Age/Sex	Triggers	Skin lesions	Serum tryptase (ng/mL)	Percent MCs in BM core biopsy	>25% MCs in BM spindle-shaped or with atypical morphology	<i>KIT</i> D816V mutation	MC CD25 ⁺ /CD2 ⁺
Pollyea et al. (this work)	61/M	<i>Vespula maculifrons</i> <i>Triatoma protracta</i> , <i>Rhipicephalus sanguineus</i>	No	12.2	~5	Yes	No	Yes ^a /No
Bonadonna et al. (2009) ¹⁹	46/M	Hymenoptera ^b	No	27	0	No	No	Yes/NT
	62/M	Hymenoptera ^b (<i>Vespula</i> species)	No	23.3	0	No	Yes	No/NT
	51/M	Hymenoptera ^b (<i>Vespula</i> species)	No	17.4	0	No	<i>KIT</i> D816H	No/NT
	55/M	Hymenoptera (<i>Vespula</i> species)	No	12.7	0 ^c	No	No	Yes ^d /NT
	69/M	Hymenoptera (<i>Vespula</i> species)	No	16.6	0	Yes	NT	Yes ^d /NT
	51/M	Hymenoptera (<i>Vespula</i> species)	No	23.8	0	No	No	Yes ^d /NT
	69/M	Hymenoptera (<i>Vespula</i> species)	No	18.4	0	No	Yes	NT/NT
	41/M	Hymenoptera (<i>Vespula</i> species)	No	13.2	NT	Yes	No ^e	Yes ^d /NT
	32/M	Hymenoptera (<i>Polistes dominulus</i>)	No	17.6	0 ^c	Yes	No	Yes ^d /NT
Sonneck et al. (2007) ¹⁵	39/F	Hymenoptera	No	12	<1	Yes	No	Yes ^a /No
Akin et al. (2007) ¹⁶	45/M	Unknown	No	12.7	N/A	Yes	No	Yes ^a /NT
	42/M	Hymenoptera (<i>Vespula</i> species)	No	8.11	N/A	Yes	NT	Yes ^a /NT

MC, mast cell; BM, bone marrow; M, male; F, female; NT, not tested; N/A, not available.

^a By immunohistochemistry.

^b Patients exhibited "systemic symptoms" but not anaphylaxis.

^c Subdiagnostic mast cell infiltrate.

^d By flow cytometry.

^e M541L *KIT* polymorphism.

marrow cellularity (Figs. 1B–D). Flow cytometry immunophenotyping confirmed expression of partial CD25 on mast cells. The karyotype was normal. Both the biopsy and the aspirate were negative for the *KIT* D816V mutation by a modified version of allele-specific PCR [13].

Our patient only met two of the three required minor diagnostic criteria for SM, but had life-threatening anaphylactic reactions with supporting evidence of a clonal population of MCs. Although multifocal dense infiltrates of mast cells (a major criterion for SM) were not observed in the bone marrow, there was clear evidence of a loosely clustered population of spindle-shaped mast cells which were tryptase, CD117, and CD25-positive, comprising about 5% of the bone marrow. Spindle-shaped CD25-positive mast cells are characteristic of SM with the *KIT* D816V mutation, and in this case provide indirect evidence of a clonal population even in the absence of a confirmatory genetic mutation [14].

Recently, an additional SM subcategory, monoclonal mast cell activation syndrome (MMAS), has been proposed for patients such as the one presented, with evidence of a clonal mast cell-related disorder but do not meet WHO criteria for SM [15]. There may be a spectrum of SM, and accordingly, this diagnosis has been proposed to classify patients like ours with recurrent anaphylaxis of unknown etiology without skin lesions and at least one (excluding elevated tryptase level), but less than three, minor criteria required for SM [15]. More specific consensus criteria to diagnose MMAS have not yet been established.

Because of the relatively low mast cell burden we could not rule out the possibility that the absence of the *KIT* D816V mutation was a false negative result. This would be supported by the finding that sorting for CD25⁺ cells allowed detection of the mutation in several cases in which unsorted cells yielded a negative result [16]. In addition, it is possible that this monoclonal population has not yet developed the *KIT* mutation, or that another activating *KIT* mutation is responsible for the clonal population, which has been observed in a low proportion of patients with SM [17–19]. Emerging techniques such as single-cell laser capture

micro-dissection may provide better sensitivity in isolating abnormal mast cells with a suspected *KIT* mutation [20]; however, this method was not utilized in this case.

In the original paper that proposed the diagnosis of MMAS, one patient who experienced unexplained severe hypotension after a hymenoptera sting was described who met diagnostic criteria [15]. She was a 39-year-old female who lacked skin lesions, but was diagnosed with urticaria pigmentosa in early childhood, which disappeared before puberty. Her bone marrow revealed no compact MC infiltrates, her serum tryptase was 12 ng/mL, and she was negative for the *KIT* D816V mutation in the bone marrow. However, >25% of her bone marrow MCs were spindle shaped, and her MCs expressed CD25 [15]. Akin et al. reported two patients with idiopathic anaphylaxis who lacked urticaria pigmentosa skin lesions and bone marrow MC aggregates [16]. Both had CD25 positive MCs which were morphologically abnormal [6]. One patient was negative for the *KIT* D816V mutation and one was not tested; this latter patient clearly may have met criteria for SM if all the relevant data were available, but in the absence of this information, could be considered to have MMAS. Bonadonna and colleagues identified 379 patients with systemic reactions to Hymenoptera venom and found 44 (11.6%) to have elevated serum tryptase levels at baseline [19]. Bone marrow biopsies with flow cytometry and *KIT* mutation analysis were performed in 34 patients, resulting in a clinicopathologic diagnosis of indolent SM in 21 patients (62%) and MMAS in nine individuals (27%). Of the nine MMAS patients, three had "systemic symptoms" and six had anaphylaxis caused by Hymenoptera venom, with a median baseline serum tryptase level of 17.6 ng/mL (range 12.7–23.8 ng/mL) [19]. All known reported cases of MMAS are summarized in Table II.

It has been recommended that patients with MMAS warrant the same treatment as would be utilized for SM with anaphylaxis, [15] and our allergist colleagues agreed with our recommendation that the patient prophylactically take an H1 antihistamine (loratadine), H2 antihistamine (ranitidine) and a leukotriene inhibitor (montelukast). They also suggested he continue to carry subcutaneous epinephrine, as well as prednisone and

diphenhydramine for use in the event of further insect encounters. In addition, out of concern that the yellow jacket venom-specific IgE could represent a more traditional allergy, even in the absence of a positive skin test, the allergists initiated yellow jacket venom immunotherapy. He was started at one-tenth the usual starting dose (0.05 mL of venom, concentration 0.001 mcg/mL). He is being administered weekly doses, doubling each dose and increasing the concentration by 10-fold each month until he reaches a final monthly dose of 1 mL at a concentration of 100 mcg/mL. We urged our patient to avoid known anaphylactic triggers, but he would not consider moving from his heavily wooded property. Instead, he opted to continue to perform his summer yard work in a full body bee-keepers suit, and to sleep in a carefully maintained tent in his bedroom.

Because of the life-threatening nature of this condition, it is important to consider a diagnosis of MMAS in patients who present with a clinical picture consistent with SM but do not meet WHO criteria, as doing so may promote interventions that can decrease morbidity and mortality. Patients with unexplained anaphylactic symptoms and an increased baseline serum tryptase level should be referred to a hematologist to consider the possibility of an occult mast cell disorder and a work-up including a bone marrow examination.

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