

Mastocytosis and allergy

Matthew Greenhawt and Cem Akin

Purpose of review

To illustrate features of allergy in mastocytosis.

Recent findings

The rates of atopy in patients with mastocytosis have generally been found to be similar to those of the normal population, although the incidence of anaphylaxis is much higher in mastocytosis. Introduction of objective pathologic criteria by the WHO for the diagnosis of mastocytosis has greatly facilitated the workup of patients with suspected mastocytosis, and has led to identification of mast cell disease in a subset of patients with anaphylaxis. There is increasing evidence that an activating c-kit mutation (D816V) exists in a subset of patients with recurrent mast cell activation symptoms who have normal-appearing bone marrow biopsies in routine evaluations without skin lesions. The genetic deficiency of α tryptase has not been found to influence serum tryptase levels in patients with mastocytosis.

Summary

Pathologic mast cell activation is a key finding in both allergic diseases and mastocytosis, albeit caused by entirely different mechanisms. Mastocytosis should be suspected in patients with recurrent anaphylaxis, who present with syncopal or near-syncopal episodes without associated hives or angioedema.

Keywords

anaphylaxis, c-kit, Hymenoptera, mastocytosis, tryptase

Introduction

Immunoglobulin E (IgE)-mediated mast cell activation is central to development of symptoms of allergic disease. Symptoms due to mast cell mediator release are also often encountered in mastocytosis, a primary disorder of mast cells resulting in increased numbers and activation of these cells in tissues such as skin and bone marrow [1]. Although pathogenesis of mastocytosis is, at least in part, mediated by an activation mutation in the c-kit gene [2[•]], and, as such, is entirely different from that of allergic disorders, symptoms in both disease states may show some degree of overlap due to mast cell mediator release [3]. Establishment of well defined objective diagnostic criteria for mastocytosis has greatly facilitated the diagnostic workup of patients presenting with unexplained symptoms attributable to mast cell mediator release [4,5]. It should be kept in perspective, however, that allergic diseases are far more common than mastocytosis, and a patient may thus have coexisting atopic disease complicating management of mastocytosis. This article will review general features of allergy in mastocytosis as well as conditions that are encountered by the practicing allergist that may lead to consideration of mastocytosis in differential diagnosis.

Mastocytosis: more than skin deep

A case report by Nettleship and Tay in 1869 [6] described a 2-year-old child with 'chronic urticaria' who had a 'peculiar eruption leaving stains of a light brown color' since 3 months of age. We now know the case described as a 'rare form of urticaria' in this report was the first published observation of cutaneous mastocytosis, a disorder bearing no resemblance in its morphology or etiology to what we know as urticaria today. Mastocytosis is classified into seven categories according to pathologic and clinical findings (Table 1) [4,5,7^{••}]. Cutaneous mastocytosis is characterized by the presence of skin lesions (most commonly urticaria pigmentosa as described in the initial case report) in the absence of bone marrow or other internal organ infiltration by mast cells. This category of mastocytosis is generally seen in children and has a good prognosis with most patients experiencing regression or improvement of skin lesions by adolescence [8]. Cutaneous mastocytosis should not be confused with adult-onset urticaria pigmentosa, which is commonly associated with systemic mastocytosis. Systemic mastocytosis is a clonal proliferative disorder of mast cells that causes pathological accumulation of mast cells in various tissues. Symptoms of systemic mastocytosis range along a continuum of mild to severe, and can affect virtually any

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Division of Allergy and Immunology, Department of Internal Medicine, University of Michigan, School of Medicine, Ann Arbor, Michigan, USA

Correspondence to Cem Akin, MD, PhD, University of Michigan, 1150 West Medical Center Drive, 5520-B, MSRB-1, Box 0600, Ann Arbor, MI 48109, USA
Tel: +1 734 647 6234; fax: +1 734 763 4151; e-mail: cemakin@umich.edu

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Abbreviation

IgE immunoglobulin E

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Table 1 Classification of mastocytosis

Category	Notes
Cutaneous mastocytosis	Most common in children. No bone marrow involvement. Good prognosis. Resolves or improves by adolescence in most patients. Serum tryptase generally <20 ng/ml
Indolent systemic mastocytosis	Most common category in adults. May or may not present with skin involvement. Serum tryptase generally >20 ng/ml. Good prognosis in most patients. Symptomatic treatment. Associated hematologic disorders must be ruled out
Systemic mastocytosis with associated clonal hematological nonmast cell lineage disease	Generally associated with chronic myeloproliferative disorders, and myelodysplastic syndromes, but can also be observed with acute myeloid leukemia, and lymphoproliferative disorders. Prognosis depends on the associated hematologic disorder
Aggressive systemic mastocytosis	Destructive mast cell infiltration associates with signs of end-organ dysfunction, such as cytopenias, ascites, malabsorption and pathologic bone fractures. Rare category. Poor prognosis
Mast cell leukemia	Presence of mast cells >10% in peripheral blood or >20% in bone marrow aspirate smears with high-grade morphology. Extremely rare. Tryptase levels markedly elevated. Poor prognosis.
Mast cell sarcoma	Malignant, invasive solid mast cell tumor. Rare. Poor prognosis
Extracutaneous mastocytoma	Benign mast cell tumor in an extracutaneous tissue. Rare

For a detailed discussion of diagnostic criteria and classification of mastocytosis, see Refs [4,5,7**].

organ in the body. The hallmark of diagnosis is identification of a collection of mast cells carrying aberrant features, typically in perivascular areas, that have positive immunohistochemical staining for tryptase or positive metachromatic staining for Giemsa or toluidine blue. The WHO published diagnostic criteria for mastocytosis in 2001 based on the recommendations of an earlier consensus conference [4,5]. To establish a formal diagnosis of systemic mastocytosis, one major criterion and one minor criterion, or three minor criteria are required. Mast cell infiltrates in aggregates of greater than 15 found in a tissue other than skin (typically bone marrow) comprise the major criterion. Minor criteria are elevated serum tryptase greater than 20 ng/ml, abnormal mast cell morphology (spindle-shaped appearance, abnormal granulation, or cytoplasmic projections), surface staining of mast cells for CD2 and CD25, and detection of a codon 816 *c-kit* mutation in lesional tissue. Most biopsies are obtained from bone marrow for evaluation for systemic mastocytosis, although other tissues may also reveal pathology occasionally. Once the diagnosis of systemic mastocytosis is made, the patient should be classified into a disease category. Indolent systemic mastocytosis is the most common category in adult patients and generally has a good prognosis, although some forms may have an aggressive course with poorer prognosis. A detailed consensus report on recommendations for diagnostic evaluation and management of patients with mastocytosis has recently been published [7**].

In contrast to systemic mastocytosis, there are no well defined pathologic criteria for diagnosis of cutaneous mastocytosis. This diagnosis is generally established by an experienced physician after observation of typical lesions of urticaria pigmentosa or mastocytoma [9]. Skin biopsies show increased numbers of mast cells (generally more than 20 mast cells per high power field) in the absence of other inflammatory cells, particularly in the upper dermis around blood vessels. One should avoid diagnosing cutaneous mastocytosis based on a blind skin biopsy or biopsy of a skin lesion that does

not have the morphologic appearance of urticaria pigmentosa or mastocytoma.

Patients in all categories of mastocytosis often experience symptoms resulting from inappropriate release of mediators contained in the cytoplasmic granules or synthesized *de novo* after mast cell activation [10]. Preformed mediators contained in cytoplasmic mast cell granules include histamine, tryptase, chymase, carboxypeptidase, and heparin. Lipid-derived mediators such as prostaglandin D2 and leukotriene C4, as well as proinflammatory cytokines platelet activating factor, interleukin (IL)-5, IL-6, transforming growth factor- β , and tumor necrosis factor- α are also formed after mast cell activation [3]. Systemic symptoms may include hypotension, recurrent syncope or presyncope, flushing, headaches, itching, abdominal pain, dyspepsia, diarrhea, bone and soft tissue pain, and cognitive problems [11*]. In aggressive mastocytosis, anticoagulation, wasting, ascites and signs of an associated bone marrow failure may be seen. Mast cell mediator release in mastocytosis typically occurs through a non-IgE-mediated mechanism, at times triggered by physical stimuli such as temperature changes, pressure and exercise, certain medications and anesthetic agents, venoms, emotional stress, and contrast dyes.

A gain-of-function mutation in the tyrosine kinase domain of KIT (most commonly D816V), a transmembrane receptor which critically regulates mast cell growth, differentiation and survival, is found in almost all patients with systemic mastocytosis and in some with cutaneous mastocytosis [2*,12,13]. It is not known, however, whether the mast cell mediator release encountered in mastocytosis is due to an intrinsic defect lowering of the activation threshold of mast cells or is simply a result of abnormal accumulation. Interestingly, the amount of mast cell burden does not always correlate with the severity of mast cell mediator release symptoms, suggesting that factors other than increased mast cell numbers are involved.

Common clinical scenarios prompting a referral to an allergist for mastocytosis

Diagnosis of mastocytosis is easily made in patients presenting with urticaria pigmentosa or cutaneous mastocytosis. Up to 20% of patients (mainly in adult population), however, are diagnosed with mastocytosis without any skin lesions. It is this latter group that generally presents a diagnostic challenge. Patients with advanced categories of mastocytosis are more likely to present without skin lesions. Recent reports described a group of patients with recurrent anaphylaxis who lacked urticaria pigmentosa and had minimal changes in bone marrow biopsy but met two or more minor criteria for systemic mastocytosis (see below) [14,15]. Often, persons with systemic or even cutaneous mastocytosis go undiagnosed or unrecognized for a period of time. Symptoms can masquerade as many different entities, including allergic reactions, pseudoallergic reactions, cardiac disorders, gastrointestinal disorders, vasculitis, endocrinologic disorders, or idiopathic conditions [11[•]]. When clinical suspicion arises, typically a serum tryptase is the appropriate starting point for testing, although mastocytosis can still be diagnosed in the absence of elevated baseline tryptase levels in a small number of patients [16].

Elevated serum tryptase level

Tryptase, a tetrameric serine protease, is a central component of the preformed mast cell granules [17]. Approximately 90% of the enzymatic activity noted from the release of mast cell mediators is attributable to tryptase, though its exact biological significance has yet to be identified. There are at least four genes encoding for tryptases in the human genome: α , β , γ and δ [18]. Tryptases detectable in circulation are mainly the products of α and β genes. Both tryptases are initially produced as proenzymes and only β but not α tryptase gets processed to the mature enzyme and retained in mast cell granules, while proenzymes (α and pro- β) are constitutively secreted outside of the mast cell, making up the bulk of detectable baseline tryptase in the circulation. Mature (β) tryptase, however, is a reliable marker for mast cell degranulation, and can serve as a surrogate marker of anaphylaxis, if it is assayed within 4 h of the event. A recent case report describes a patient with idiopathic anaphylaxis who had an elevated tryptase level measured 26 h after the anaphylactic episode, suggesting that there may be individual differences in tryptase kinetics in circulation [19]. Conversely, tryptase levels may not be found to be elevated in all patients after anaphylactic episodes, especially due to food allergy, for unclear reasons [20]. Approximately a quarter of the general population lack the α tryptase gene [21], however this deficiency is not reflected in measurable tryptase levels in mastocytosis patients in a clinically meaningful way [22]. Interestingly, elevated tryptase

levels were associated with increased prothrombin and partial thromboplastin times in a recent study [22], but clinically significant coagulation defects after mast cell activation are generally limited to disease variants with extensive mast cell burden.

Generally accepted reference cutoff levels for the upper limit of normal serum tryptase are approximately 12–14 ng/ml, and a tryptase level greater than 20 ng/ml is a minor diagnostic criterion for systemic mastocytosis [17]. This level has greater than 80% sensitivity and 98% specificity for mastocytosis [23,24]. It should be noted that serum tryptase levels are normal in many cases of cutaneous mastocytosis, generally seen in children. Similarly, despite their high sensitivity and specificity, elevations in serum tryptase are not exclusively pathognomonic for systemic mastocytosis. Elevated levels of tryptase can be seen in myeloproliferative disorders, in chronic eosinophilic leukemia associated with *FIP1L1/PDGFR α* mutation, as well as in end-stage renal disease, onchocerciasis while in the treatment stage, amniotic fluid embolism, sudden infant death syndrome and postural orthostatic tachycardia syndrome [17,25–29]. Furthermore, normal mast cells can be found in increased numbers (reactive hyperplasia) in tissues in many inflammatory and neoplastic disorders, which may theoretically cause mild to moderate elevations in serum tryptase.

Hymenoptera venom anaphylaxis

A link between mastocytosis and systemic reactions to the Hymenoptera venoms is well established [30–32]. There is no shortage of case reports in the medical literature describing severe anaphylactic events secondary to insect stings that were met with suspicion of an underlying process, only to discover the patient has some form of mastocytosis. Approximately 7–11% of persons with Hymenoptera allergy show elevated basal tryptase levels, and these patients are more likely to have profound systemic reactions after stings than those with normal tryptase levels, more so to vesperula than honeybee venoms [31,33]. Such patients with elevated baseline serum tryptase levels may have very few or no urticaria pigmentosa lesions, and may have negative radioallergen sorbent test (RAST) or skin tests to venoms [31,34]. These observations implicate mast cell disease as a risk factor for a severe allergic reaction to Hymenoptera venom.

Although there are no guidelines for management of this patient population, most experts would recommend a trial of venom immunotherapy in these patients, especially if they have a positive venom skin test or RAST. The optimal duration of immunotherapy in this patient population has also not been established. There are reports of fatalities after Hymenoptera stings in mastocytosis after discontinuation of venom immunotherapy [35]. Some experts thus recommend lifelong venom immunotherapy

to protect against adverse outcomes from an accidental sting [31]. Patients with elevated baseline tryptase levels or mastocytosis have been reported to tolerate venom immunotherapy well [36], although one study found this patient group was also more likely to react to sting challenge after venom immunotherapy, indicating incomplete protection [31]. Therefore, continued carrying of self-injectable epinephrine is recommended for this patient population, regardless of institution of venom immunotherapy.

Flushing and rashes

Flushing is the result of cutaneous vascular smooth muscle dilatation, creating a sensation of warmth accompanied by visible reddening [37^{••}]. Typically, the areas most affected by flushing are the face, neck, upper chest, and upper extremities, although any area of the body can be affected. Both episodic and constant flushing has a wide differential diagnosis of causes ranging from normal physiologic causes to abnormal disease states [37^{••},38]. Benign/physiologic causes include fever, emotion/anxiety, hyperthermia, rosacea, food/beverage, alcohol, menopause and benign cutaneous flushing. Pathologic causes include carcinoid syndrome, pheochromocytoma, mastocytosis, anaphylaxis, thyroid carcinoma, VIPoma, neurologic disease, and medications. Flushing in mastocytosis is often episodic with duration generally limited to less than a few hours, is caused by the vasoactive substances released from the preformed granules, may be induced by alcohol, exercise, warm temperatures, and stress, and seen in association with other mast cell degranulation symptoms such as abdominal pain, lightheadedness, hypotension, and sometimes nasal and ocular symptoms. Constant painful flushing not associated with other mast cell degranulation symptoms in the absence of cutaneous mastocytosis is not typically observed in mastocytosis.

Mastocytosis, in both systemic and cutaneous forms, is associated with several skin manifestations. Urticaria pigmentosa, the most common form of mastocytosis, is described as a fixed hyperpigmented (red-brown), maculopapular rash generally sparing sun-exposed areas [9,39,40]. The adult form of urticaria pigmentosa typically consists of more numerous, smaller lesions that can become more confluent and mottled over the trunk and thighs. In children, urticaria pigmentosa is more demarcated, with larger sized lesions, very rarely confluent, and can form blisters in the first 3 years of life [8]. Typically, urticaria pigmentosa lesions can show Darier's sign, or development of a wheal and flare after these lesions are lightly stroked. While patients with mastocytosis can also show dermatographism, this latter condition is much more common, affecting up to 5% of the general population [41], and does not necessarily indicate the presence of a mast cell disease in most patients. Patients with mastocytosis do not have higher incidence of chronic or

acute urticaria, although children with mastocytoma have been known to develop generalized hives after physical irritation of the lesion [42]. Similarly, recurrent angioedema, eczematous rashes or 'multiple chemical or drug sensitivities' are not sufficient reasons to suspect a diagnosis of mastocytosis.

Recurrent anaphylaxis

Mast cell degranulation in systemic mastocytosis can cause cardiovascular and circulatory symptoms that could be mistaken for idiopathic anaphylaxis [43]. A recent study on 601 patients with anaphylaxis from a tertiary referral center over 25 years reported that 59% of the cases were considered idiopathic [44[•]]. For reference, 33% of the patient population examined in this latter study reported syncope, 25% flushing, 15% hypotension, and 6% reported chest pain. Urticaria, angioedema and wheezing are more frequently associated with idiopathic anaphylaxis than mastocytosis.

A recent study conducted on patients with recurrent unexplained anaphylaxis who did not have urticaria pigmentosa and had a 'normal' appearing bone marrow biopsy with no mast cell clusters (major diagnostic criterion) showed the presence of clonal mast cell markers such as D816V c-kit mutation and CD25 expression in five out of 12 patients [45]. Most of these patients also had a normal or only slightly elevated tryptase levels. The relatively high incidence of mast cell disease in patients with unexplained anaphylaxis in this study suggests that a bone marrow biopsy should be seriously considered in every patient with recurrent anaphylaxis regardless of skin findings or tryptase levels. Mast cell disease may be particularly subtle in patients with normal or slightly elevated tryptase levels, and referral to a tertiary research center with experience in mast cell disorders should be considered for this patient population, who may show only one or two minor diagnostic criteria. Monoclonal mast cell activation disorder has been proposed as a new term to define this patient population who meet only one or two minor diagnostic criteria for systemic mastocytosis [15]. It is not clear whether these patients will develop full diagnostic criteria of mastocytosis with time, but limited follow up in our cohort suggests that this may be a distinct disease subtype (C. Akin, personal observation). We have recently described a patient with food-dependent exercise-induced anaphylaxis carrying c-kit mutation in the CD25+ mast cell population, but with no other detectable criteria of mast cell disease [46]. These observations warrant a closer look at underlying mast cell disease in these poorly understood anaphylactic syndromes.

General features of allergy in mastocytosis

Although mastocytosis is not an atopic disease, allergic diseases are common in the general population and may

coexist in patients with mastocytosis. An early retrospective study in the USA on the natural course of urticaria pigmentosa reported 44% of patients to have a personal or family history (in siblings, parents or grandparents) of hay fever or asthma [47]. Another study on 33 Swiss patients with urticaria pigmentosa found 21% to have symptoms of allergic disease [48]. This group included six allergic rhinitis, two bronchial asthma, one food allergy, six drug allergy, five urticaria and five Hymenoptera allergy, but no atopic dermatitis cases. In our series of 67 patients with urticaria pigmentosa, 31% reported a history consistent with atopic disease [49]. Interestingly, patients with atopic disease tended to have fewer lesions than those without atopy. A recent study from Spain addressed the frequency of allergic disease in a population of 210 patients with cutaneous or systemic mastocytosis and found the prevalence of allergy to be 23.9%, based on allergen skin testing or demonstration of specific IgE correlating with symptoms [50]. Thirty-six patients had anaphylaxis, which was mediated by specific IgE in nine. Drug anaphylaxis can be the initial presenting symptom in mastocytosis [51]. Incriminating medications may include NSAIDs, antibiotics, angiotensin-converting enzyme inhibitors, general anesthetics, opioids and muscle relaxants.

Collectively, the literature suggests that the incidence of atopy in patients with mastocytosis is comparable to the general population, while the incidence of anaphylactic mast cell degranulation (IgE or non-IgE mediated) in mastocytosis is significantly higher [52]. Total IgE levels are generally found to be decreased in mastocytosis, presumably due to the capture by increased mast cell burden [48]. Medical management of allergic disease should follow the same general guidelines as for patients without mastocytosis, with the caveat that there are no data on safety and efficacy of allergen immunotherapy in patients with mastocytosis. Therefore, in our opinion, this treatment modality should be reserved for patients in whom the benefits clearly outweigh the risks, such as those with anaphylactic sensitivity to hymenoptera venoms.

Conclusion

Mastocytosis is a rare condition associated with abnormal accumulation of mast cells in various organs, often associated with a point mutation that serves as a marker of clonal abnormal myeloproliferation. Symptoms affect virtually every organ system of the body, but most commonly involve pruritis, flushing, gastrointestinal pain, and cardiovascular collapse in the most severe cases. Prompt recognition of symptoms is important to counsel patients, so that appropriate treatment can be initiated and triggers of mast cell mediator release can be avoided.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 454–455).

- 1 Akin C, Metcalfe DD. Systemic mastocytosis. *Annu Rev Med* 2004; 55: 419–432.
- 2 Akin C. Molecular diagnosis of mast cell disorders: a paper from the 2005 William Beaumont Hospital Symposium on Molecular Pathology. *J Mol Diagn* 2006; 8:412–419.
- A discussion on the methodologic aspects and potential pitfalls of the mutational analysis of the c-kit gene in mastocytosis.
- 3 Castells M. Mast cell mediators in allergic inflammation and mastocytosis. *Immunol Allergy Clin North Am* 2006; 26:465–485.
- 4 Valent P, Horny H, Escribano L, *et al.* Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001; 25:603–625.
- 5 Valent P, Horny HP, Li CY, *et al.* Mastocytosis. In: Jaffe ES, Harris NL, Stein H, *et al.*, editors. *World Health Organization classification of tumours: pathology and genetics of tumours of the haematopoietic and lymphoid tissues*. Lyon: IARC Press; 2001. pp. 291–302.
- 6 Nettleship E, Tay W. Rare forms of urticaria. *BMJ* 1869; 2:323.
- 7 Valent P, Akin C, Escribano L, *et al.* Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations, and response criteria. *Eur J Clin Invest* 2007; 37:435–453.
- An excellent review summarizing the recommendations for various aspects of diagnostic evaluation and management of patients with mastocytosis.
- 8 Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002; 86: 315–319.
- 9 Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. *Leuk Res* 2001; 25:519–528.
- 10 Escribano L, Akin C, Castells M, *et al.* Current options in the treatment of mast cell mediator-related symptoms in mastocytosis. *Inflamm Allergy Drug Targets* 2006; 5:61–77.
- 11 Butterfield JH. Systemic mastocytosis: clinical manifestations and differential diagnosis. *Immunol Allergy Clin North Am* 2006; 26:487–513.
- A comprehensive overview of differential diagnosis of symptoms in patients presenting with suspected mastocytosis. Helps in understanding why the diagnosis of mastocytosis cannot be based on symptoms alone.
- 12 Nagata H, Worobec AS, Oh CK, *et al.* Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc Natl Acad Sci USA* 1995; 92:10560–10564.
- 13 Sotlar K, Escribano L, Landt O, *et al.* One-step detection of c-kit point mutations using peptide nucleic acid-mediated polymerase chain reaction clamping and hybridization probes. *Am J Pathol* 2003; 162:737–746.
- 14 Akin C, Metcalfe DD. Occult bone marrow mastocytosis presenting as recurrent systemic anaphylaxis [abstract]. *J Allergy Clin Immunol* 2003; 111:S206.
- 15 Sonneck K, Florian S, Mullauer L, *et al.* Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol* 2007; 142:158–164.
- 16 Akin C, Schwartz LB, Kitoh T, *et al.* Soluble stem cell factor receptor (CD117) and IL-2 receptor alpha chain (CD25) levels in the plasma of patients with mastocytosis: relationships to disease severity and bone marrow pathology. *Blood* 2000; 96:1267–1273.
- 17 Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006; 26:451–463.
- 18 Caughey GH. Tryptase genetics and anaphylaxis. *J Allergy Clin Immunol* 2006; 117:1411–1414.
- 19 Shanmugam G, Schwartz LB, Khan DA. Prolonged elevation of serum tryptase in idiopathic anaphylaxis. *J Allergy Clin Immunol* 2006; 117:950–951.
- 20 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327:380–384.
- 21 Soto D, Malmsten C, Blount JL, *et al.* Genetic deficiency of human mast cell alpha-tryptase. *Clin Exp Allergy* 2002; 32:1000–1006.
- 22 Akin C, Soto D, Brittain E, *et al.* Tryptase haplotype in mastocytosis: relationship to disease variant and diagnostic utility of total tryptase levels. *Clin Immunol* 2007; 123:268–271.

- 23 Schwartz LB, Sakai K, Bradford TR, *et al.* The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. *J Clin Invest* 1995; 96:2702–2710.
- 24 Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders. *Leuk Res* 2001; 25:553–562.
- 25 Hsieh FH, Alam MM, Lichtin AE. Elevated total serum tryptase levels in patients with postural orthostatic tachicardia syndrome (POTS): a case series [abstract]. *J Allergy Clin Immunol* 2005; 115:S248.
- 26 Buckley MG, Variend S, Walls AF. Elevated serum concentrations of beta-tryptase, but not alpha-tryptase, in sudden infant death syndrome (SIDS): an investigation of anaphylactic mechanisms. *Clin Exp Allergy* 2001; 31:1696–1704.
- 27 Klion AD, Noel P, Akin C, *et al.* Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 2003; 101:4660–4666.
- 28 Sperr WR, Jordan JH, Baghestanian M, *et al.* Expression of mast cell tryptase by myeloblasts in a group of patients with acute myeloid leukemia. *Blood* 2001; 98:2200–2209.
- 29 Sperr WR, Jordan JH, Stehberger B, *et al.* Detection of elevated serum tryptase levels in MDS. *Blood* 1999; 94:287b.
- 30 Kors JW, van Doormaal JJ, de Monchy JG. Anaphylactoid shock following Hymenoptera sting as a presenting symptom of systemic mastocytosis. *J Intern Med* 1993; 233:255–258.
- 31 Haeblerli G, Bronnimann M, Hunziker T, *et al.* Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. *Clin Exp Allergy* 2003; 33: 1216–1220.
- 32 Rueff F, Placzek M, Przybilla B. Mastocytosis and Hymenoptera venom allergy. *Curr Opin Allergy Clin Immunol* 2006; 6:284–288.
- 33 Ludolph-Hauser D, Rueff F, Fries C, *et al.* Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. *Lancet* 2001; 357:361–362.
- 34 Kranke B, Sturm G, Aberer W. Negative venom skin test results and mastocytosis. *J Allergy Clin Immunol* 2004; 113:180–181.
- 35 Oude Elberink JN, de Monchy JG, Kors JW, *et al.* Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. *J Allergy Clin Immunol* 1997; 99:153–154.
- 36 Fricker M, Helbling A, Schwartz L, *et al.* Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 1997; 100:11–15.
- 37 Izikson L, English JC 3rd, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. *J Am Acad Dermatol* 2006; 55:193–208. Detailed discussion of various flushing syndromes.
- 38 Metcalfe DD. Differential diagnosis of the patient with unexplained flushing/anaphylaxis. *Allergy Asthma Proc* 2000; 21:21–24.
- 39 Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; 144:682–695.
- 40 Brockow K. Urticaria pigmentosa. *Immunol Allergy Clin North Am* 2004; 24:287–316.
- 41 Taskapan O, Harmanyeri Y. Evaluation of patients with symptomatic dermographism. *J Eur Acad Dermatol Venereol* 2006; 20:58–62.
- 42 McClelland VM, Brookfield DS. Palpation reveals the diagnosis. *Arch Dis Child* 2005; 90:1278.
- 43 Ditto AM, Harris KE, Krasnick J, *et al.* Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996; 77:285–291.
- 44 Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006; 97:39–43.
- Large case series from a tertiary referral center for anaphylaxis.
- 45 Akin C, Scott LM, Kocabas CN, *et al.* Demonstration of an aberrant mast cell population with clonal markers in a subset of patients with idiopathic anaphylaxis. *Blood* 2007, in press.
- 46 Hungness SI, Singer AM, Akin C. Food-dependent exercise-induced anaphylaxis associated with clonal mast cells carrying an activating c-kit mutation [abstract]. *J Allergy Clin Immunol* 2007; 119:S29.
- 47 Caplan RM. The natural course of urticaria pigmentosa: analysis and follow-up of 112 cases. *Arch Dermatol* 1963; 87:146–157.
- 48 Muller U, Helbling A, Hunziker T, *et al.* Mastocytosis and atopy: a study of 33 patients with urticaria pigmentosa. *Allergy* 1990; 45:597–603.
- 49 Brockow K, Akin C, Huber M, *et al.* Assessment of the extent of cutaneous involvement in children and adults with mastocytosis: relationship to symptomatology, tryptase levels, and bone marrow pathology. *J Am Acad Dermatol* 2003; 48:508–516.
- 50 Gonzales de Olano D, de la Hoz Caballer MB, Nunez-Lopez R, *et al.* Prevalence of allergy and anaphylaxis in 210 patients with mastocytosis: a study from the Spanish network on mastocytosis (REMA) [abstract]. *J Allergy Clin Immunol* 2007; 119:S28.
- 51 Codreanu F, Morisset M, Renaudin JM, *et al.* Drug anaphylaxis as presentation of systemic mastocytosis: about 7 case reports [abstract]. *J Allergy Clin Immunol* 2007; 119:S28.
- 52 Brockow K, Jofer C, Ring J. Anaphylaxis in patients with mastocytosis: a prospective study on prevalence, severity and trigger factors in 121 patients [abstract]. *J Allergy Clin Immunol* 2006; 117:S307.